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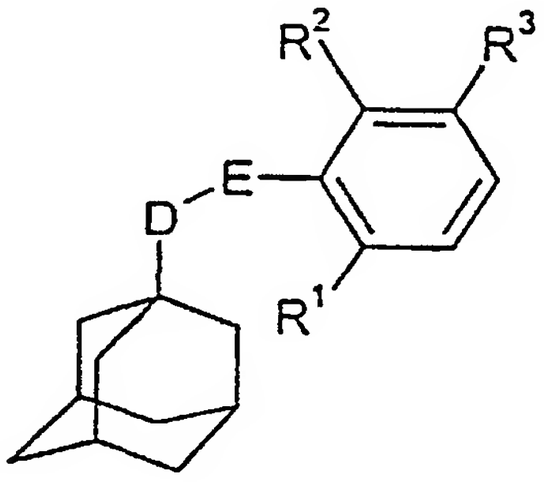
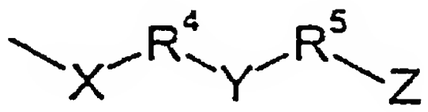
(54) Title: ADAMANTANE DERIVATIVES



(I)



(II)

(57) Abstract: The invention provides adamantane derivatives of formula (I), a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

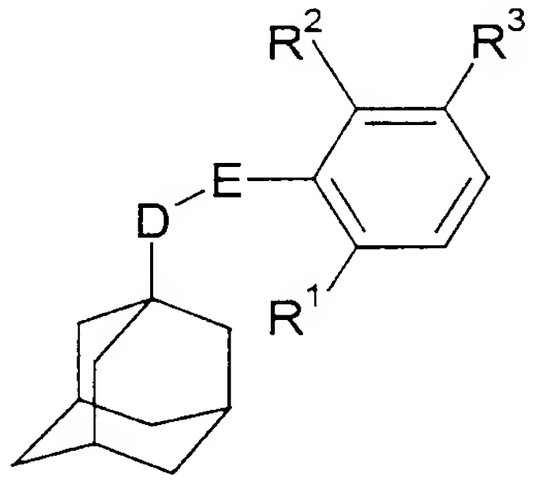
Adamantane derivatives

The present invention relates to adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

The $P2X_7$ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the $P2X_7$ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1β (IL-1β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and L-selectin shedding (lymphocytes). $P2X_7$ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes, erythrocytes, erythroleukaemic cells, monocytes, fibroblasts, bone marrow cells, neurones and renal mesangial cells.

It would be desirable to make compounds effective as $P2X_7$ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the $P2X_7$ receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of general formula



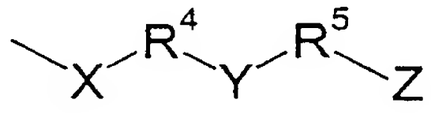
(I)

wherein D represents CH_2 or CH_2CH_2, preferably CH_2;

E represents C(O)NH or, preferably, NHC(O);

R^1 and R^2 each independently represent a hydrogen or halogen (e.g. fluorine, chlorine, bromine or iodine) atom, or an amino (NH_2), nitro (NO_2), C_1-C_6 alkyl or trifluoromethyl group;

R^3 represents a group of formula



(II);

X represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y represents an oxygen or sulphur atom or a group NR^{11}, SO or SO_2;

Z represents a group -OH, -SH, $-CO_2H$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^6R^7$, $-C(O)NR^8R^9$, imidazolyl, 1-methylimidazolyl, $-N(R^{10})C(O)$-C_1-C_6 alkyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyloxy, $-OC(O)NR^{12}R^{13}$, $-OCH_2OC(O)R^{14}$, $-OCH_2OC(O)OR^{15}$ or $-OC(O)OCH_2OR^{16}$;

R^4 represents a C_2-C_6 alkyl group;

R^5 represents a C_1-C_6 alkyl group;

R^6, R^7, R^8, R^9, R^{10}, R^{12} and R^{13} each independently represent a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one hydroxyl group (e.g., one, two or three hydroxyl groups);

R^{11} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent (e.g. one, two or three substituents) independently selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14}, R^{15} and R^{16} each independently represent a C_1-C_6 alkyl group;

with the provisos that (i) when E represents NHC(O), X represents O, S or NH and Y represents O, then Z represents $-NR^6R^7$ where R^6 represents a hydrogen atom and R^7 represents either a hydrogen atom or a C_1-C_6 alkyl group substituted by at least one hydroxyl group, and (ii) when E represents NHC(O), X represents O, S or NH, Y represents NH and R^5 represents CH_2CH_2, then Z is not -OH or imidazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched. In the present invention, an alkyl group or moiety may contain up to 6 carbon atoms, examples of which include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl and n-hexyl.

Preferably, R^1 and R^2 each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1-C_4 alkyl or trifluoromethyl group.

More preferably, R^1 and R^2 each independently represent a hydrogen, chlorine or bromine atom, or an amino, nitro, C_1-C_3 alkyl or trifluoromethyl group.

Most preferably, R^1 and R^2 each independently represent a hydrogen or chlorine atom.

Preferably X represents an oxygen atom or a group NH.

Preferably Z represents a group -OH, -SH, $-CO_2H$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4-alkylsulphinyl, C_1-C_4-alkylsulphonyl, $-NR^6R^7$, $-C(O)NR^8R^9$, imidazolyl, 1-methylimidazolyl, $-N(R^{10})C(O)$-C_1-C_4 alkyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkoxycarbonyloxy, $-OC(O)NR^{12}R^{13}$, $-OCH_2OC(O)R^{14}$, $-OCH_2OC(O)OR^{15}$ or $-OC(O)OCH_2OR^{16}$.

Particularly preferred groups Z include -OH, $-CO_2H$, methoxy, methylthio, methylsulphinyl, methylsulphonyl, $-NR^6R^7$, $-C(O)NR^8R^9$, $-N(R^{10})C(O)CH_3$, imidazolyl, 1-methylimidazolyl, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkoxycarbonyloxy, $-OC(O)NR^{12}R^{13}$, $-OCH_2OC(O)R^{14}$, $-OCH_2OC(O)OR^{15}$ and $-OC(O)OCH_2OR^{16}$.

R^4 preferably represents a C_2-C_4 alkyl group, for example a linear alkyl group such as $-(CH_2)_2-$ or $-(CH_2)_3-$.

R^5 preferably represents a C_1-C_5 alkyl group, for example -CH_2-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$CH_2CH(CH_3)$-, -$CH(CH_3)CH_2$-, -$(CH_2)_2C(CH_3)_2$- or -$CH_2C(CH_3)_2$-.

Preferably R^6, R^7, R^8, R^9, R^{10}, R^{12} and R^{13} each independently represent a hydrogen atom, or a C_1-C_4 alkyl group optionally substituted by at least one hydroxyl group.

Y is conveniently a group NR^{11}. It is preferred that R^{11} represents a hydrogen atom, or a C_1-C_4 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6, preferably C_1-C_4, alkoxy.

R^{14}, R^{15} and R^{16} each independently represent a C_1-C_6 alkyl group, preferably a C_1-C_4 alkyl group.

Preferred compounds of the invention include:

2-Chloro-5-[2-(2-methoxyethylamino)ethylamino]-*N*-(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylmethyl)-benzamide, hydrochloride,

[2-[4-Chloro-3-(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylmethyl)carbamoyl-phenylamino]-ethyamino]-acetic acid, hydrochloride,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylmethyl)-benzamide, acetate,

5-[2-(2-Aminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylmethyl)-benzamide, acetate,

5-[2-(2-Acetylaminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylmethyl)-benzamide, acetate,

[2-[4-Chloro-3-(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid,

2-Chloro-5-[2-(2-methylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

2-Chloro-5-[2-(2-dimethylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

2-Chloro-5-[3-(3-hydroxypropylthio)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-[2-(2-Aminoethylthio)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[2-(3-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[3-(3-hydroxypropylsulfonyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(±)-2-Chloro-5-[3-(3-hydroxypropylsulfinyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(S)-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(R)-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(S)-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(R)-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(±)-2-Chloro-5-[2-(3-hydroxypropylsulfinyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(±)-5-[2-(2-Aminoethylsulfinyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-[2-(2-Aminoethylsulfonyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-[3-(2-Aminoethylthio)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(±)-5-[3-(2-Aminoethylsulfinyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-[3-(2-Aminoethylsulfonyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[[2-[(3-hydroxy-3-methylbutyl)amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[[2-[[2-(methylthio)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(methylsulfinyl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetic acid salt,

2-Chloro-5-[2-[(2-hydroxy-2-methylpropyl)amino]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide, dihydrochloride,

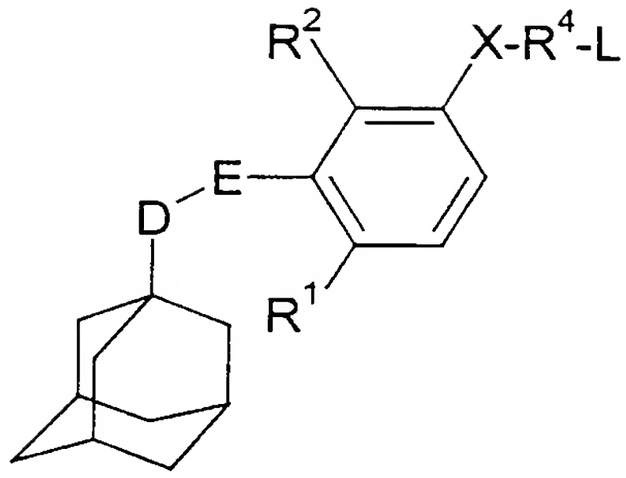
2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-5-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, and

2-Chloro-5-[[2-[[3-(1*H*-imidazol-1-yl)propyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises:

a) when Y represents an oxygen or sulphur atom or a group NR^{11}, reacting a compound of general formula



(III)

wherein L represents a leaving group (e.g. a halogen atom) and D, E, R^1, R^2, X and R^4 are as defined in formula (I), with a compound of general formula

$$R^{20}—R^5—Z \quad \text{(IV)}$$

wherein R^{20} represents –OH, -SH or –NHR^{11} and R^5, R^{11} and Z are as defined in formula (I); or

b) when Y represents SO or SO_2, reacting a corresponding compound of formula (I) in which Y represents a sulphur atom with a suitable oxidising agent;

and optionally after (a) or (b) converting the compound of formula (I) obtained to a pharmaceutically acceptable salt or solvate thereof.

The processes of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as dichloromethane, tetrahydrofuran, or an alcohol such a ethanol, isopropanol or butanol, at a temperature, e.g. in the range from 0 to 200 °C, preferably in the range from 0 to 150 °C. The oxidising agent used in (b) above may, for example, be 3-chloroperoxybenzoic acid or potassium peroxymonosulphate, commercially sold under the trade mark "OXONE".

Compounds of formula (III) are either known in the art, e.g. from WO 99/29660 and WO 99/29661 or may be prepared easily using known techniques. Compounds of formula (III) wherein X is an oxygen atom can be prepared from the corresponding phenol

(WO 99/29660 and WO 99/29661) and a haloalkanol such as 2-chloroethanol, 3-chloropropanol or 4-chlorobutanol in the presence of triphenylphosphine and diethyl azodicarboxylate. Compounds of formula (III) wherein X is an NH group can be prepared from the corresponding aniline (WO 99/29660 and WO 99/29661) and a haloalkanal such as chloroacetaldehyde, 4-chlorobutanal, 5-chloropentanal or an appropriately protected hydroxyalkanal such as 3-*tert*-butyldimethylsilyloxypropanal in the presence of a reducing agent such as sodium triacetoxyborohydride. In the latter case, removal of the protecting group and activation, for example by conversion into the mesylate group affords compounds of formula (III). Compounds of formula (III) wherein X is a sulfur atom can be prepared from the corresponding thiophenol in the presence of a dihaloalkane such as 1-bromo-2-chloroethane, 1-bromo-3-chloropropane or 1-bromo-4-chlorobutane in the presence of a base such as cesium carbonate.

Compounds of formula (IV) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl, carboxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve at a certain stage the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate,

methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the present invention are advantageous in that they possess pharmacological activity and have utility as modulators of $P2X_7$ receptor activity. They are therefore indicated as pharmaceuticals for use in the treatment or prevention of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, hyperresponsiveness of the airway, chronic obstructive pulmonary disease (COPD), bronchitis, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, neurodegenerative disease, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischaemic heart disease, stroke, peripheral vascular disease and varicose veins.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis, psoriasis, pulmonary disease, e.g. COPD or bronchitis, or diseases of the central nervous system, e.g. Alzheimer's disease or stroke) which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disease or condition indicated. For effecting immunosuppression, the daily dosage of the compound of formula (I) will typically be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

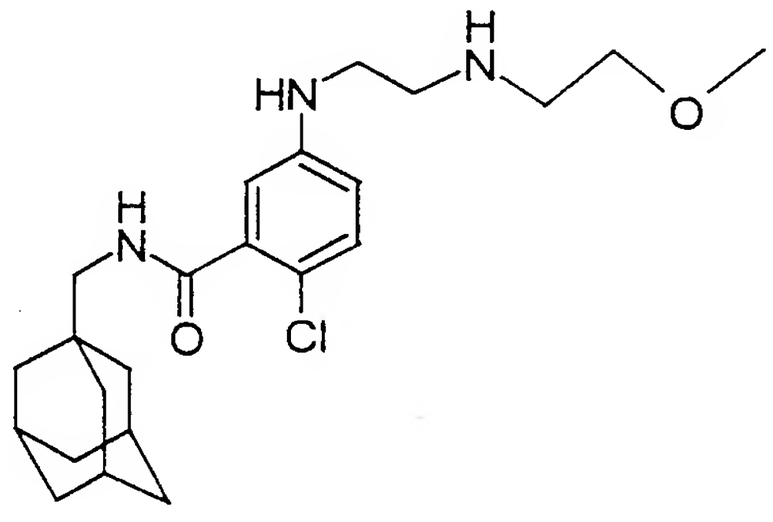
The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will now be further explained by reference to the following illustrative examples.

Example 1

2-Chloro-5-[2-(2-methoxyethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



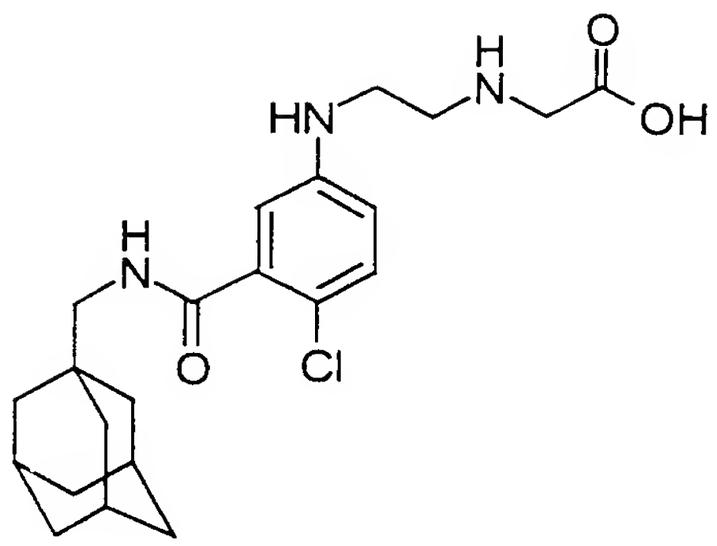
To a solution of 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.2 g) and *N,N*-diisopropylethylamine (0.27 ml) in ethanol (5 ml) was added sodium iodide (0.08 g) and 2-methoxyethylamine (0.11 g). The reaction vessel was sealed and the reaction mixture heated at 90 °C for 15h before concentration under reduced pressure. The residue was partitioned between ethyl acetate and sodium hydrogencarbonate solution, and the aqueous phase extracted with additional ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by NPHPLC (eluting with 0-25% ethanol in dichloromethane) to afford 5-(*N*-(2-methoxyethyl)-2-aminoethyl)amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide as a semi-solid. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure to leave the title compound as a white solid (0.085 g).

MS (APCI +ve) 420/422 $(M+H)^+$

^{1}H NMR (CD_3OD) δ 8.27 (1H, t); 7.20(1H, d); 7.73 (2H, m); 3.63 (2H, t); 3.46 (2H, t); 3.40 (3H, s); 3.26 (2H, m); 3.04 (2H, d); 1.98 (3H, s); 1.77 (3H, d); 1.67 (3H, d); 1.62 (6H, s).

Example 2

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, hydrochloride



a) [2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 1 using 2-chloro-5-(2-chloroethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.2 g) and *tert*butyl glycine (0.26 g) to deliver the sub-title compound as a brown foam (0.10 g).

^{1}H NMR (CD_3OD) δ 7.13 (1H, d); 6.66 (2H, m); 3.20 (2H, t); 3.02 (2H, s); 2.79 (2H, t); 1.97 (3H, s); 1.76 (3H, d); 1.72 (3H, d); 1.61 (6H, s); 1.43 (9H, s).

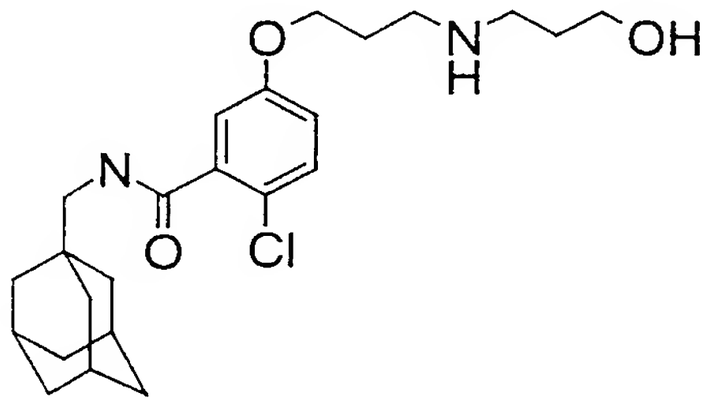
b) [2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, hydrochloride

To [2-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-acetic acid, 1,1-dimethylethyl ester (0.10 g, Example 2a) was added a solution of HCl in dioxane (5 ml of a 4M solution) and reaction mixture stirred at room temperature for 48h before concentration under reduced pressure. The residue was recrystallised twice from propan-2-ol/ethyl acetate/ether mixture to afford the title compound as a white solid (0.006 g).

^{1}H NMR (CD_3OD) δ 8.30 (1H, t); 7.20 (1H, d); 6.72 (2H, m); 3.94 (2H, s); 3.47 (2H, s); 3.28 (2H, m); 3.03 (2H, s); 1.97 (3H, s); 1.76 (3H, d); 1.68 (3H, d); 1.61 (6H, s).

Example 3

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) 2-Chloro-5-[3-chloropropoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

To a solution of 2-chloro-5-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.48 g) in ethanol (5 ml) was added caesium carbonate (0.977 g) and reaction mixture heated to 85 °C for 10min. before addition of 1-bromo-3-chloropropane (0.74 ml). Heating was continued for 24h before cooling to room temperature and concentration under reduced pressure. The residue was dissolved in ethyl acetate and washed with water(twice), then with $KHSO_4$ solution and brine. The organics were dried ($MgSO_4$), concentrated and the residue purified by silica gel chromatography (eluting with 20% ethyl acetate in isohexanes) to deliver the sub-title compound as a pale yellow foam (0.50 g).

^{1}H NMR ($CDCl_3$) δ 7.28 (2H, m); 6.91 (1H, m); 6.34 (1H, t); 4.13 (2H, t); 3.73 (2H, t); 3.58 (2H, d); 2.23 (2H, tt); 2.10 (2H, d); 1.73 (3H, d); 1.65 (3H, d); 1.59 (6H, s).

b) 2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

To a solution of 2-chloro-5-[3-chloropropoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.25 g, Example 3a) and *N,N*-diisopropylethylamine (0.54 ml) in ethanol (5 ml) was added sodium iodide (0.08 g) and 1-propanolamine (0.24 ml). The reaction vessel was sealed and reaction mixture heated at 120 °C for 24h. The reaction mixture was then concentrated under reduced pressure. The residue was partitioned between ethyl acetate

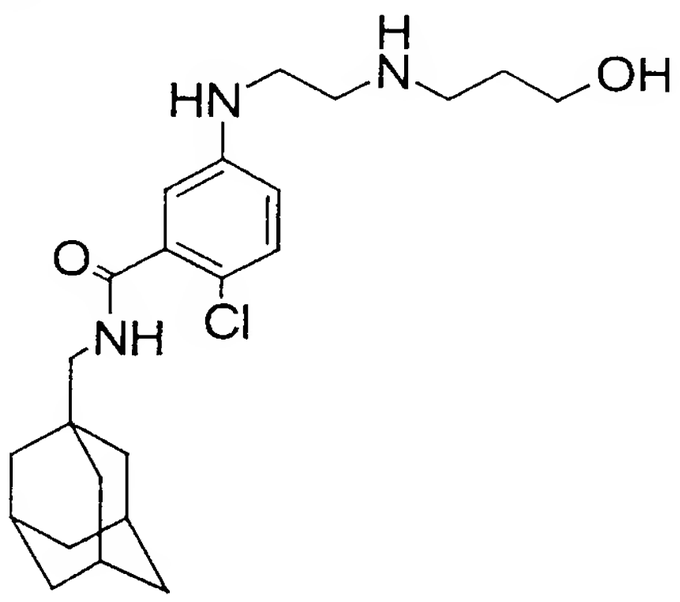
and sodium hydrogencarbonate solution, and the aqueous phase extracted with additional ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by NPHPLC (eluting with 0-25% ethanol in dichloromethane) to give 2-chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide as a semi-solid. This compound was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure to leave the title compound as a white solid (0.036 g).

MS (APCI +ve) 435/437 (M+H)+

^{1}H NMR (CD_3OD) δ 8.28 (1H, t); 7.27 (1H, d); 6.93 (2H, m); 4.05 (2H, t); 3.62 (2H, t); 3.15 (2H, m); 3.09 (2H, t); 2.96 (2H, m); 2.10 (2H, tt); 1.89 (3H, s); 1.82 (2H, tt); 1.68 (3H, d); 1.59 (3H, d); 1.53 (6H, s).

Example 4

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



To a solution of 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.2 g) and *N,N*-diisopropylethylamine (0.5 ml) in 1-butanol (10 ml) was added sodium iodide (0.08 g) and 3-aminopropan-1-ol (0.12 g). The reaction vessel was sealed and the reaction mixture heated at 110 °C for 15h before being concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with of 0-100% ethanol in dichloromethane with 1%

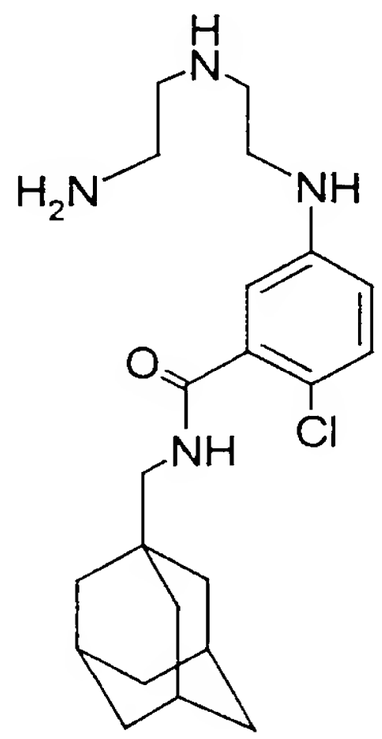
triethylamine), and further purified by RPHPLC (eluting with 15-95% MeCN in 0.1% $AcONH_4$ aqueous), to afford the title compound as a solid (0.035 g).

MS (APCI +ve) 376/378 $(M+H)^+$

^1H NMR ($CDCl_3$) δ 7.12 (1H, d); 6.88 (1H, d); 6.58 (1H, dd); 6.52 (1H, s); 4.20-4.80 (4H+water, s); 3.71 (2H, s); 3.38 (2H, d); 3.12 (2H, d); 2.99-3.05 (4H, m); 1.99 (3H, s); 1.97 (3H, s); 1.81 (2H, quin); 1.68 (6H, q); 1.57 (6H, s).

Example 5

5-[2-(2-Aminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



a) [2-[2-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenylamino]-ethylamino]ethyl]-carbamic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.2 g) and (2-amino-ethyl)-carbamic acid tert butyl ester (0.25 g) to deliver the sub-title compound as a brown oil (0.25 g).

MS (APCI +ve) 405/407 $(M+H\text{-Boc})^+$

b) 5-[2-(2-Aminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate

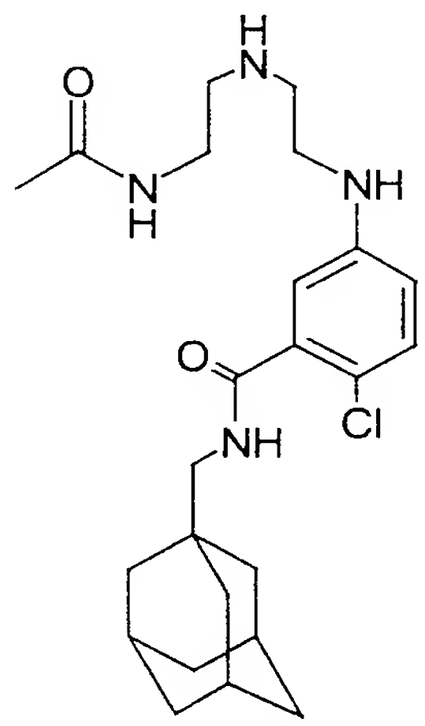
4M HCl in dioxane (2ml) was added to a solution of [2-[2-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenylamino]-ethylamino]ethyl]-carbamic acid, 1,1-dimethylethyl ester (0.25g, Example 5a) in isopropanol (5ml). After 15h the reaction mixture was concentrated and the residue purified by RPHPLC (eluting with 15-95% MeCN in 0.1% $AcONH_4$ aqueous) to afford the title compound as a solid (0.035g).

MS (APCI +ve) 405/407 $(M+H)^+$

^1H NMR ($CDCl_3$) δ 7.12 (1H, d); 7.00 (1H, d); 6.61 (1H, dd); 6.50 (1H, t); 3.28 (2H, s); 3.10 (2H, d); 3.02 (2H, s); 2.95 (4H, s); 2.20-2.80 (5H+water, s); 1.99 (6H, s); 1.68 (6H, q); 1.57 (6H, s).

Example 6

5-[2-(2-Acetylaminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



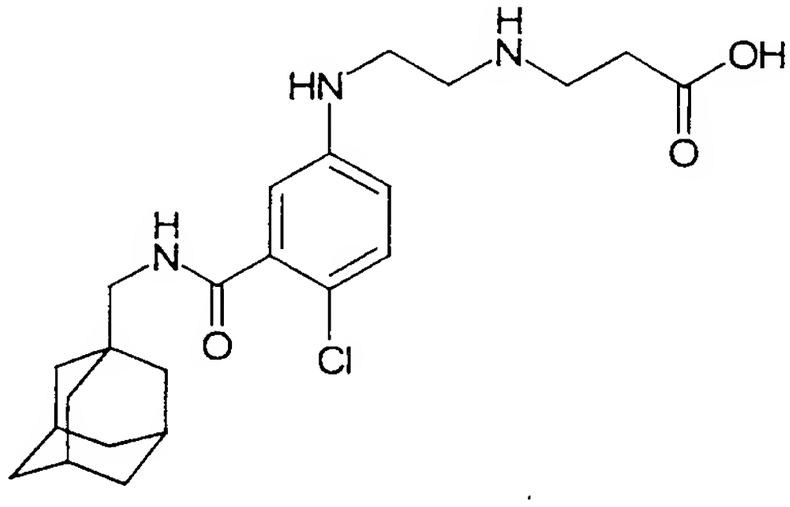
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.2g) and *N*-(2-amino-ethyl)-acetamide (0.16g) to deliver the title compound as a solid (0.03g).

MS (APCI +ve) 447/449 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.15 (1H, d); 6.95 (1H, d); 6.68 (1H, s); 6.60 (1H, dd); 6.47 (1H, t); 3.41 (2H, q); 3.33 (2H, t); 3.15 (2H, d); 2.99 (2H, t); 2.87 (2H, t); 2.20-2.60 (3H+water, s); 1.99 (3H, s); 1.98 (3H, s); 1.95 (3H, s); 1.68 (6H, q); 1.58 (6H, s).

Example 7

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid



a) [2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.2 g) and β-alanine 1,1-dimethylethyl ester (0.29 g) to deliver the sub-title compound as an oil (0.20 g).

MS (APCI +ve) 490/492 $(M+H)^+$

b) [2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid

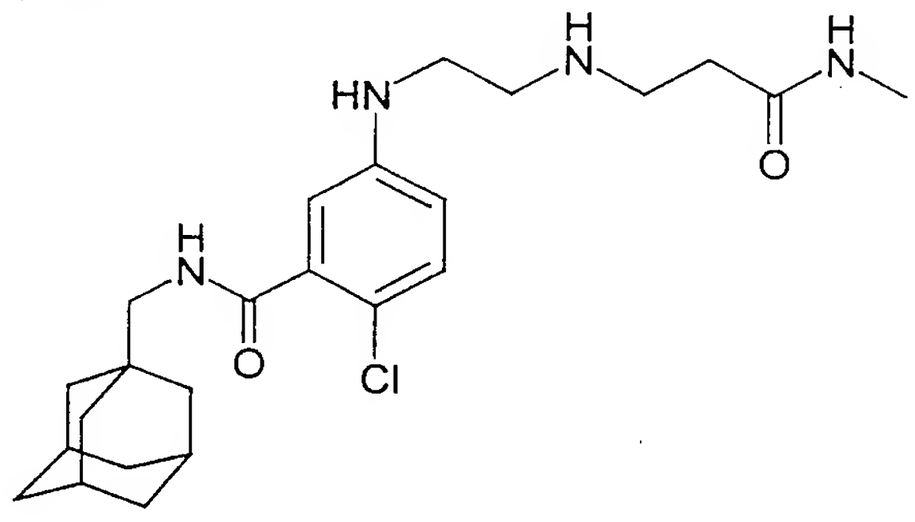
To a solution of [2-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid, 1,1-dimethylethyl ester (0.20 g, Example 7a) in dichloromethane (5ml), was added trifluoroacetic acid (2 ml). After 15h the solution was concentrated and purified by RPHPLC (eluting with 15-95% MeCN in 0.1% $AcONH_4$ aqueous) to afford the title compound as a solid (0.010 g).

MS (APCI +ve) 434/436 $(M+H)^+$

^{1}H NMR ($CDCl_3$/d_6-DMSO/d_1-TFA/CD_3OD) δ 7.18 (1H, d); 6.78 (1H, d); 6.68 (1H, dd); 3.50 (2H, t); 3.25 (2H, t); 3.22 (2H, t); 3.10 (2H, s); 2.78 (2H, t); 2.00 (3H, s); 1.69 (6H, q); 1.59 (6H, s).

Example 8

2-Chloro-5-[2-(2-methylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



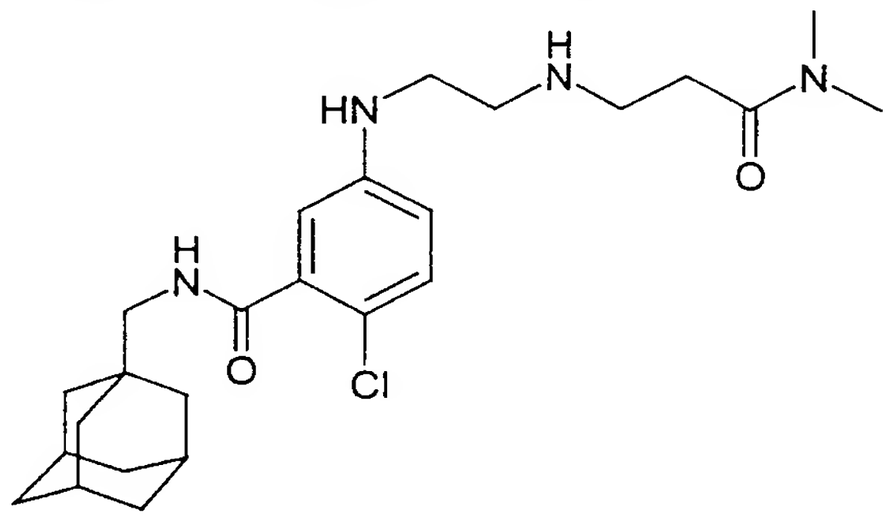
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.2g) (0.2 g) and 3-amino-*N*-methylpropionamide (0.22 g) to give the title compound (0.08g).

MS (APCI +ve) 447/449 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.13 (1H, d); 6.90 (1H, d); 6.59 (1H, dd); 6.20-6.40 (5H+water, m); 3.40 (2H, t); 3.14 (2H, d); 3.08-3.01 (4H, m); 2.73 (2H, d); 2.52 (2H, t); 2.00 (6H, s); 1.68 (6H, q); 1.58 (6H, s).

Example 9

2-Chloro-5-[2-(2-dimethylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate



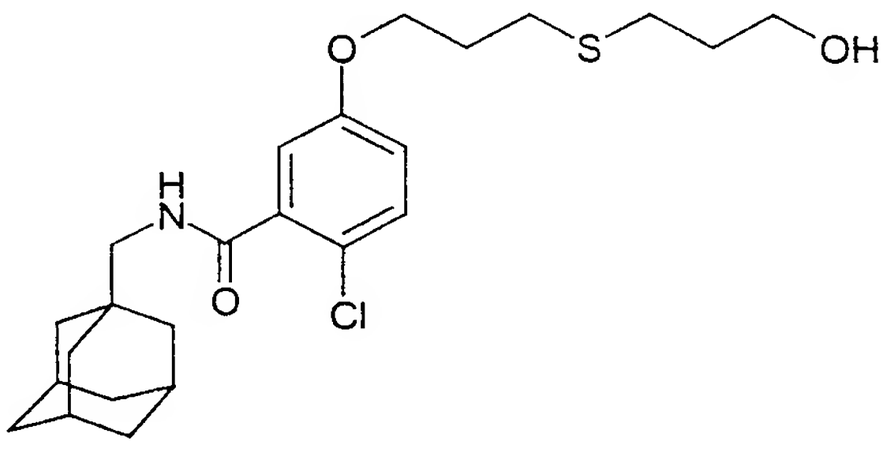
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.2g) (0.2 g) and 3-amino-*N,N*-dimethylpropionamide (0.23 g) to deliver the title compound (0.005 g).

MS (APCI +ve) 461/463 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.14 (1H, d); 6.95 (1H, d); 6.63 (1H, dd); 6.37 (1H, t); 3.35 (2H, t); 3.16 (2H, d); 3.02-2.99 (7H, m); 2.94 (3H, s); 2.63 (2H, t); 2.60-2.20 (3H+water, s); 2.05 (3H, s); 2.00 (3H, s); 1.69 (6H, q); 1.58 (6H, s).

Example 10

2-Chloro-5-[3-(3-hydroxypropylthio)propoxy]- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



To a solution of 2-chloro-5-[3-chloropropoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.06 g, Example 3a) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.07 ml) in

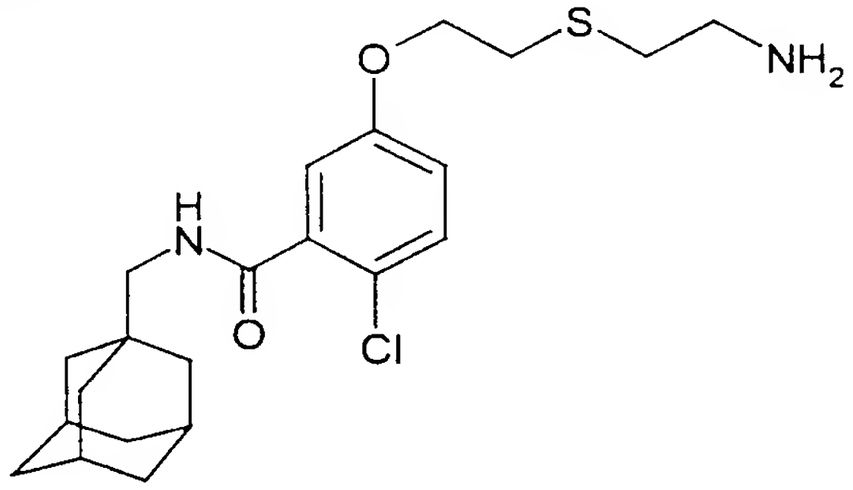
1-butanol (5 ml) was added sodium iodide (0.023 g) and 3-mecaptopropan-1-ol (0.04 ml). The reaction vessel was sealed and the mixture heated at 100 °C for 24h. The reaction mixture was diluted with ethyl acetate and washed twice with 2M hydrochloric acid, twice with sodium hydrogencarbonate solution and once with brine. The organics were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by NPHPLC (eluting with 0-2% ethanol in dichloromethane) to leave the title compound as a white solid (0.05g).

MS (APCI +ve) 452/454 $(M+H)^+$

^1H NMR ($CDCl_3$) δ 7.29-7.26 (2H, m); 6.90 (1H, dd); 6.36 (1H, t); 4.09 (2H, t); 3.76 (2H, q); 3.17 (2H, d); 2.71 (2H, t); 2.65 (2H, t); 2.06 (2H, quin); 2.00 (3H, s); 1.85 (2H, quin); 1.69 (6H, q); 1.58 (6H, s).

Example 11

5-[2-(2-Aminoethylthio)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) 2-Chloro-5-[2-chloroethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

To a solution of 2-chloro-5-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO 99/29661) (0.30 g), triphenylphosphine (0.25 g) and 2-chloroethanol (0.07 ml) in tetrahydrofuran (4 ml) was added diethyl azodicarboxylate (0.15 ml) and the reaction mixture stirred at room temperature for 18h. Further triphenylphosphine (0.12 g) and diethyl azodicarboxylate (0.08 ml) were added and the reaction stirred for an additional 4h. Silica was added and the reaction mixture concentrated under reduced pressure. The

residue was purified by silica gel chromatography (eluting with 20% ethyl acetate in isohexanes) to deliver the sub-title compound as a lightly coloured oil (0.31 g).

^{1}H NMR (d_6-DMSO) δ 8.30 (1H, t); 7.39 (1H, d); 7.03 (1H, dd); 6.96 (1H, d); 4.29 (2H, t); 4.04 (2H, t); 2.92 (2H, d); 1.93 (3H, s); 1.72-1.44 (12H, m).

b) [2-[3-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylthio]ethyl]-carbamic acid, 1,1-dimethylethyl ester

To a solution of 2-chloro-5-[2-chloroethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)—benzamide (0.1 g, Example 11a) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.12 ml) in isopropanol (3 ml) was added sodium iodide (0.04 g) and (2-mercapto-ethyl)-carbamic acid tert butyl ester (0.14 ml). The reaction vessel was sealed and the mixture heated at 100 °C for 24h. The reaction mixture was diluted with ethyl acetate and extracted twice with 2M hydrochloric acid, twice with sodium hydrogencarbonate solution and once with brine. The organics were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by NPHPLC (eluting with 0-2% ethanol in dichloromethane) to afford the sub-title compound (0.32 g).

MS (APCI +ve) 523/525 $(M+H)^+$

c) 5-[2-(2-Aminoethylthio)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

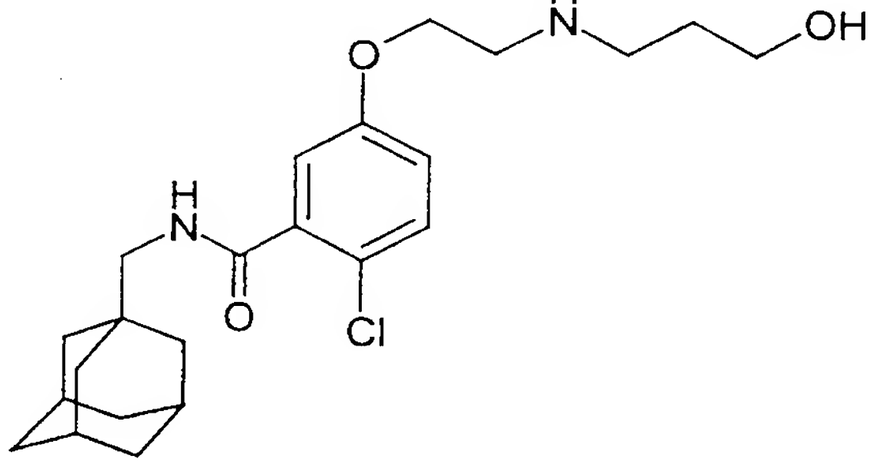
4M HCl in dioxane (2 ml) was added to a solution of [2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylthio]ethyl]-carbamic acid, 1,1-dimethylethyl ester (230 mg, Example 11b) in methanol (5 ml). After 15h the solution was concentrated then purified by RPHPLC (eluting with 15-50% MeCN in 0.1% $AcONH_4$ aqueous) to afford the title compound as the acetate salt. The acetate salt was converted to the hydrochloride salt by stirring with 4M HCl in 1,4-dioxane. Concentration and trituration with diethyl ether gave the title compound as a solid (0.055 g).

MS (APCI +ve) 423/425 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.30 (1H, t); 7.95 (3H, s); 7.39 (1H, d); 7.02 (1H, dd); 6.94 (1H, d); 4.19 (2H, t); 3.02-2.91 (6H, m); 2.85 (2H, t); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s).

Example 12

2-Chloro-5-[2-(3-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



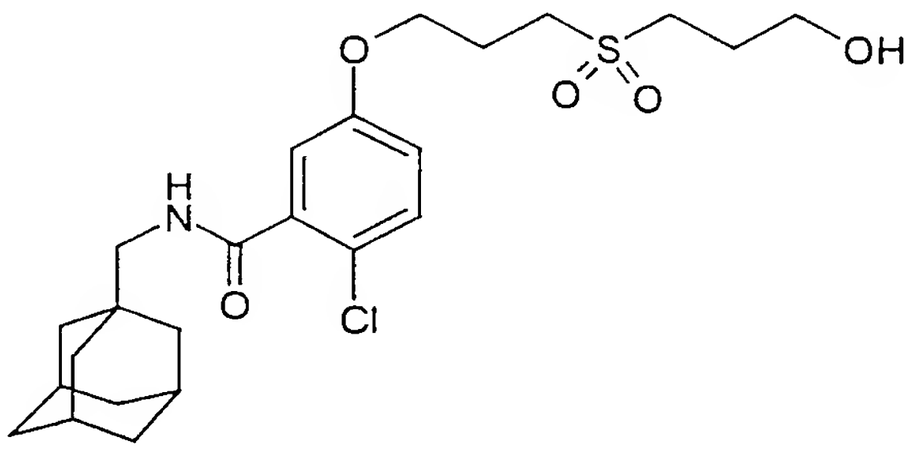
To a solution of 2-chloro-5-[2-chloroethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 11a, 0.15 g) and *N,N*-diisopropylethylamine (0.50 ml) in 1-butanol (4 ml) was added sodium iodide (0.06 g) and 3-aminopropan-1-ol (0.09 ml). The reaction vessel was sealed and the mixture heated at 110 °C for 24h. The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by RPHPLC (eluting with 25-95% MeCN / 0.1% $AcONH_4$ aqueous) to give 2-chloro-5-[2-[(3-hydroxypropyl)amino]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentration under reduced pressure. Recrystalisation from isohexane / isopropanol gave the title compound as a white solid (0.1g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.08 (2H, s); 8.32 (1H, t); 7.43 (1H, d); 7.06 (1H, dd); 6.98 (1H, d); 4.79 (1H, t); 4.27 (2H, t); 3.49 (2H, q); 3.40 (2H, s); 3.05 (2H, s); 2.93 (2H, d); 1.94 (3H, s); 1.79 (2H, quin); 1.58 (6H, q); 1.52 (6H, s).

Example 13

2-Chloro-5-[3-(3-hydroxypropylsulfonyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



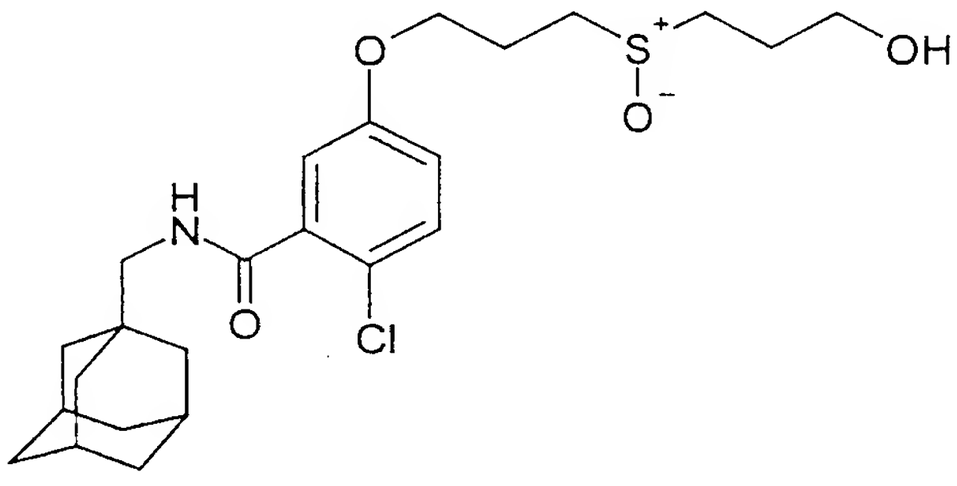
3-Chloroperoxybenzoic acid (0.14g, 70%) was added to a solution of 2-chloro-5-[3-(3-hydroxypropylthio)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 10, 0.1g) in dichloromethane (10ml). After 1 hour calcium hydroxide (0.1g) was added and stirring continued for a further 30min. The reaction mixture was dried ($MgSO_4$), filtered through celite and concentrated. The residue was triturated with ethanol to leave the title compound as a white solid (0.030g).

MS (APCI +ve) 484/486 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.29 (1H, t); 7.38 (1H, d); 7.00 (1H, dd); 6.93 (1H, d); 4.68 (1H, t); 4.11 (2H, t); 3.49 (2H, q); 3.25 (2H, t); 3.14 (2H, t); 2.92 (2H, d); 2.12 (2H, quin); 1.94 (3H, s); 1.85 (2H, quin); 1.63 (6H, q); 1.52 (6H, s).

Example 14

(±)-2-Chloro-5-[3-(3-hydroxypropylsulfinyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



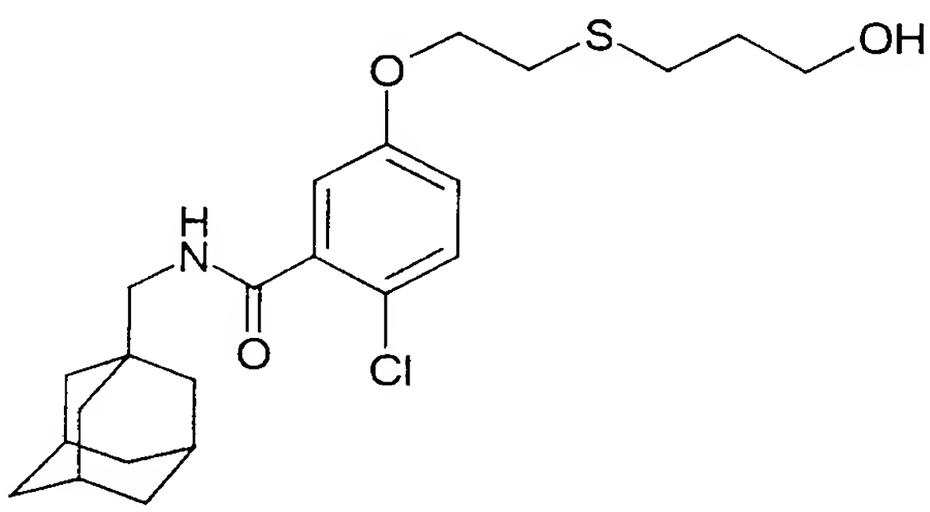
3-Chloroperoxybenzoic acid (0.065g, 70%) was added to a solution of 2-chloro-5-[3-(3-hydroxypropylthio)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 10, 0.11g) in dichloromethane (10ml). After 15h the crude reaction mixture was purified by NPHPLC (eluting 0-10% ethanol in dichloromethane) to leave the title compound as a white solid (0.055g).

MS (APCI +ve) 468/470 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.29 (1H, t); 7.37 (1H, d); 7.00 (1H, dd); 6.93 (1H, d); 4.63 (1H, t); 4.12 (2H, t); 3.50 (2H, q); 3.00-2.64 (6H, m); 2.09 (2H, quin); 1.94 (3H, s); 1.80 (2H, quin); 1.62 (6H, q); 1.52 (6H, s).

Example 15

2-Chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



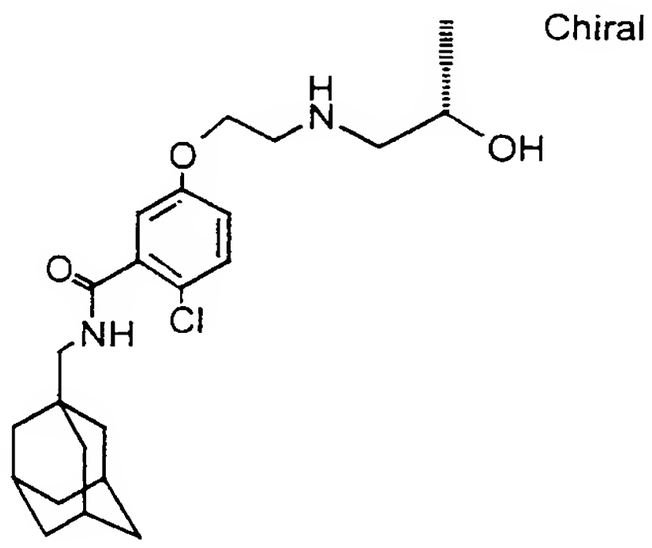
Prepared according to the method of Example 10 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 11a, 0.34g) and 3-mercaptopropan-1-ol (0.25ml) to give the title compound (0.4g).

MS (APCI +ve) 438/440 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.28 (1H, t); 7.37 (1H, d); 7.00 (1H, dd); 6.92 (1H, d); 4.47 (1H, t); 4.15 (2H, t); 3.45 (2H, q); 2.92 (2H, d); 2.86 (2H, t); 2.63 (2H, t); 1.94 (3H, s); 1.72-1.57 (8H, m); 1.51 (6H, s).

Example 16

***(S)*-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**



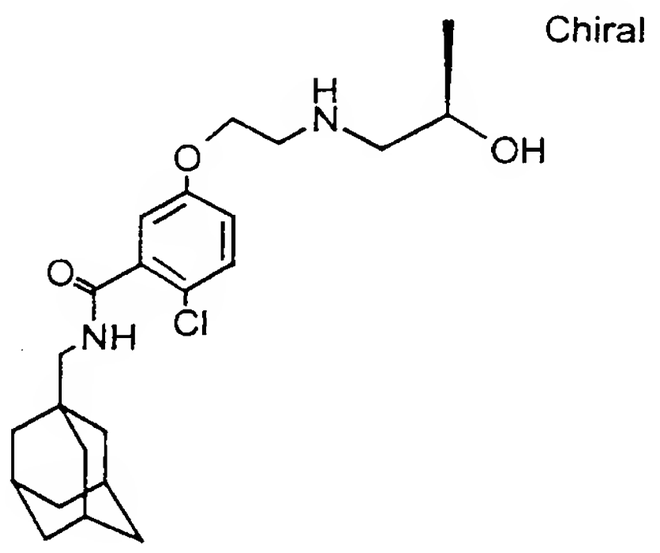
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.17 g, Example 11a) and (*S*)-1-amino-2-propanol (0.11 ml). The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) to give the title compound as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentration under reduced pressure. Recrystalisation from isohexane / isopropanol gave the title compound as a solid (0.05g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.80 (2H, d); 8.32 (1H, t); 7.42 (1H, d); 7.05 (1H, dd); 6.98 (1H, d); 5.36 (1H, d); 4.29 (2H, t); 4.05-3.95 (1H, m); 3.35 (2H, s); 3.10-3.00 (1H, m); 2.93 (2H, d); 2.85 (1H, m); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.12 (3H, d).

Example 17

***(R)*-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**



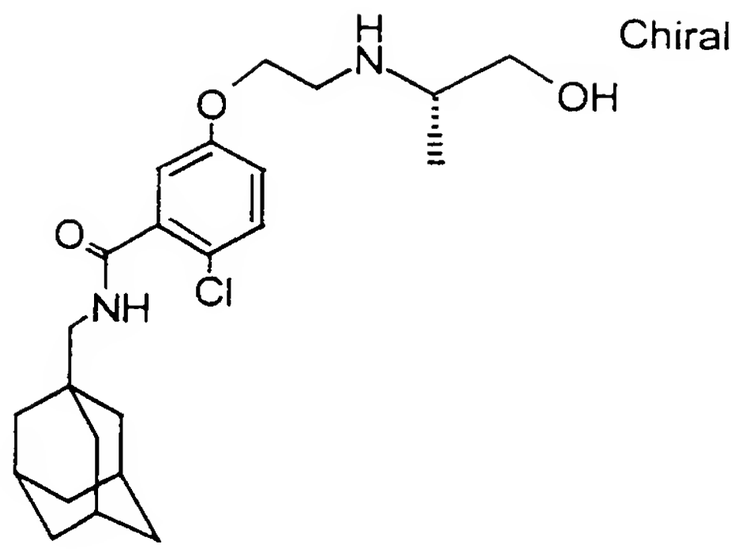
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 11a, 0.17 g) and *(R)*-1-amino-2-propanol (0.11 ml). The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) to give the title compound as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentration under reduced pressure. Trituration with diethyl ether gave the title compound as a solid (0.055g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.8 (2H, m); 8.32 (1H, t); 7.42 (1H, d); 7.05 (1H, dd); 6.98 (1H, d); 5.36 (1H, d); 4.29 (2H, t); 4.05-3.95 (1H, m); 3.35 (2H, s); 3.10-3.00 (1H, m); 2.93 (2H, d); 2.90-2.80 (1H, m); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.12 (3H, d).

Example 18

***(S)*-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**



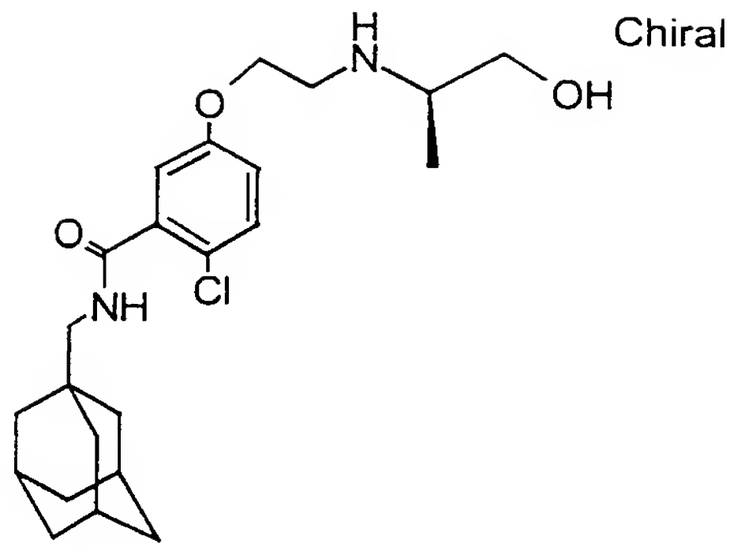
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 11a, 0.17 g) and (*S*)-2-amino-1-propanol (0.11 ml). The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) to give the title compound as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentration under reduced pressure. Trituration with diethyl ether gave the title compound as a solid (0.07g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.75 (2H, d); 8.32 (1H, t); 7.42 (1H, d); 7.05 (1H, dd); 6.99 (1H, d); 5.40 (1H, t); 4.29 (2H, t); 3.69-3.63 (1H, m); 3.56-3.50 (1H, m); 3.40-3.30 (3H+water, s); 2.93 (2H, d); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.22 (3H, d).

Example 19

***(R)*-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride**



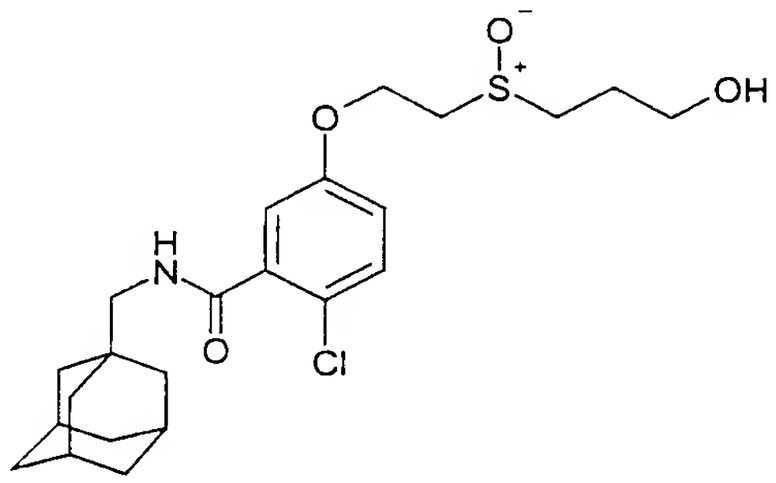
Prepared according to the method of Example 4 using 2-chloro-5-(2-chloroethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 11a, 0.17 g) and (*R*)-2-amino-1-propanol (0.11 ml). The reaction mixture was partitioned between ethyl acetate and sodium hydrogencarbonate solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by RPHPLC (eluting with 25-95% MeCN in 0.1% $AcONH_4$ aqueous) to give the title compound as the acetate salt. This was converted to the hydrochloride salt by stirring with 4M HCl in dioxane and concentrated under reduced pressure. Trituration with diethyl ether gave the title compound as a solid (0.05g).

MS (APCI +ve) 421/423 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.75 (2H, d); 8.32 (1H, t); 7.42 (1H, d); 7.05 (1H, dd); 6.99 (1H, d); 5.40 (1H, t); 4.29 (2H, t); 3.69-3.63 (1H, m); 3.56-3.50 (1H, m); 3.40-3.30 (3H+water, s); 2.93 (2H, d); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.22 (3H, d).

Example 20

(±)-2-Chloro-5-[2-(3-hydroxypropylsulfinyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



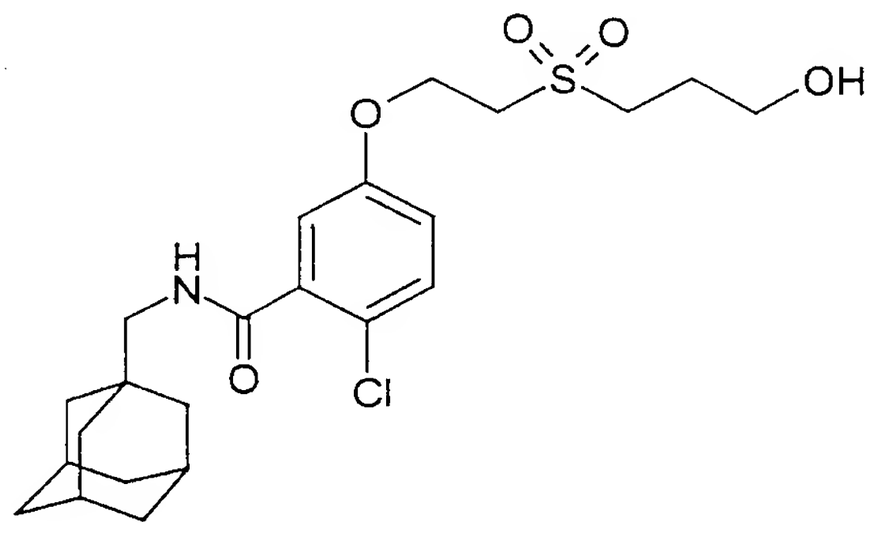
Prepared according to the method of Example 14 using 2-chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 15, 0.12g) and 3-chloroperoxybenzoic acid (0.07g, 70%) to give the title compound (0.07 g).

MS (APCI +ve) 454/456 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.31 (1H, t); 7.39 (1H, d); 7.05 (1H, dd); 6.97 (1H, d); 4.64 (1H, t); 4.30-4.50 (2H, m); 3.55 (2H, q); 3.30-3.22 (1H, m); 3.07-3.01 (1H, m); 2.93–2.83 (3H, m); 2.81-2.74 (1H, m); 1.94 (3H, s); 1.80 (2H, quin); 1.66 (6H, q); 1.52 (6H, s).

Example 21

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



Prepared according to the method of Example 13 using 2-chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example

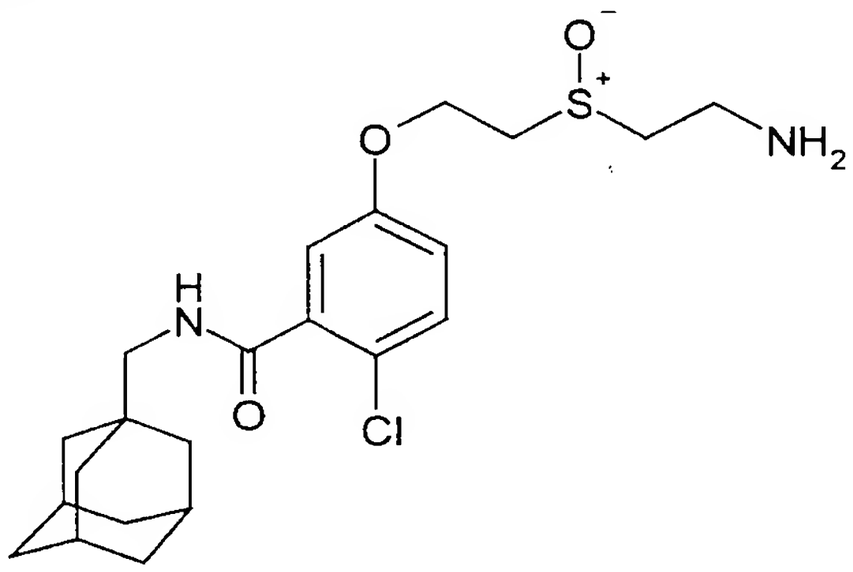
15, 0.12g) and 3-chloroperoxybenzoic acid (0.14g, 70%). Purification by NPHPLC (eluting 0-5% EtOH in dichloromethane) gave the title compound (0.07 g).

MS (APCI +ve) 470/472 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.31 (1H, t); 7.40 (1H, d); 7.05 (1H, dd); 6.98 (1H, d); 4.70 (1H, t); 4.38 (2H, t); 3.62 (2H, t); 3.50 (2H, q); 3.20 (2H, t); 2.92 (2H, d); 1.94 (3H, s); 1.85 (2H, quin); 1.66 (6H, q); 1.52 (6H, s).

Example 22

(±)-5-[2-(2-Aminoethylsulfinyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) [2-[3-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylsulfinyl]ethyl]-carbamic acid, 1,1-dimethylethyl ester

3-Chloroperoxybenzoic acid (0.1g, 70%) was added to a solution of [2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylthio]ethyl]-carbamic acid, 1,1-dimethylethyl ester (Example 11b, 0.2g) in dichloromethane (10ml). After 2h calcium hydroxide (0.3g) was added and stirring continued for a further 30minutes. The reaction mixture was dried ($MgSO_4$), filtered through celite and concentrated. Purification by NPHPLC (eluting with 0-10% ethanol in dichloromethane) gave the sub-title compound (0.14g).

MS (APCI +ve) 439/441 $(M+H\text{-}Boc)^+$

b) (±)-5-[2-(2-Aminoethylsulfinyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

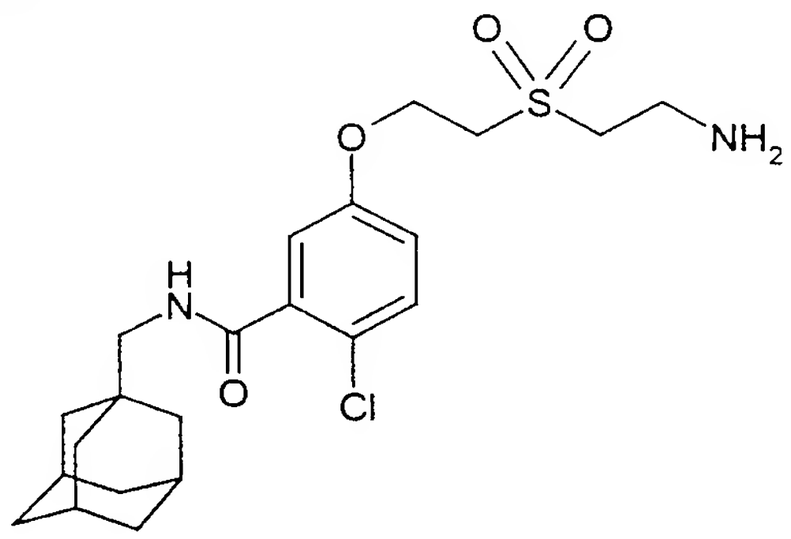
4M hydrochloric acid in dioxane (2ml) was added to a solution of [2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylsulfinyl]ethyl]-carbamic acid, 1,1-dimethylethyl ester (0.14g) in methanol (10ml). After 15h the reaction mixture was concentrated and the residue recrystallised from isohexane / isopropanol, to afford the title product (0.05g).

MS (APCI +ve) 439/441 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.32 (1H, t); 8.06 (3H, s); 7.40 (1H, d); 7.07 (1H, dd); 6.99 (1H, d); 4.45-4.30 (2H, m); 3.45-3.05 (6H, m); 2.92 (2H, d); 1.94 (3H, s); 1.85 (2H, quin); 1.63 (6H, q); 1.52 (6H, s).

Example 23

5-[2-(2-Aminoethylsulfonyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) [2-[3-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylsulfonyl]ethyl]-carbamic acid, 1,1-dimethylethyl ester

3-Chloroperoxybenzoic acid (0.3g, 70%) was added to a solution of [2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylthio]ethyl]-carbamic acid, 1,1-dimethylethyl ester (Example 11b, 0.2g) in dichloromethane (10ml). After 2h calcium hydroxide (0.3g) was added and stirring continued for a further 30min. The reaction mixture was dried ($MgSO_4$), filtered through celite and concentrated. Purification by

NPHPLC (eluting with 0-10% ethanol in dichloromethane) afforded the sub-title compound (0.12g).

MS (APCI +ve) 455/457 $(M+H-BOC)^+$

b) 5-[2-(2-Aminoethylsulfonyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

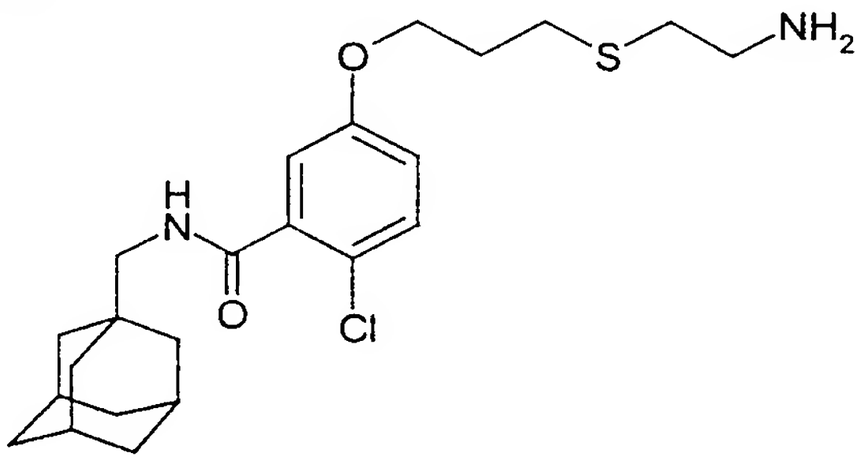
4M hydrochloric acid in dioxane (2ml) was added to a solution of [2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-ethylsulfonyl]ethyl]-carbamic acid, 1,1-dimethylethyl ester (Example 23a, 0.14g) in methanol (10ml). After 15h the reaction mixture was concentrated and the residue recrystallised from isohexane / isopropanol, to afford the title product (0.05g).

MS (APCI +ve) 455/457 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.32 (1H, t); 8.10 (3H, s); 7.42 (1H, d); 7.10 (1H, dd); 7.04 (1H, d); 4.40 (2H, t); 3.80 (2H, t); 3.55 (2H, t); 3.25 (2H, t); 2.95 (2H, d); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s).

Example 24

5-[3-(2-Aminoethylthio)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) [2-[3-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-propylthio]ethyl]-carbamic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 11b from 2-chloro-5-(3-chloropropoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 3a, 0.47g), to afford the sub-title compound (1.0g).

MS (APCI +ve) 537/539 $(M+H)^+$

b) 5-[3-(2-Aminoethylthio)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

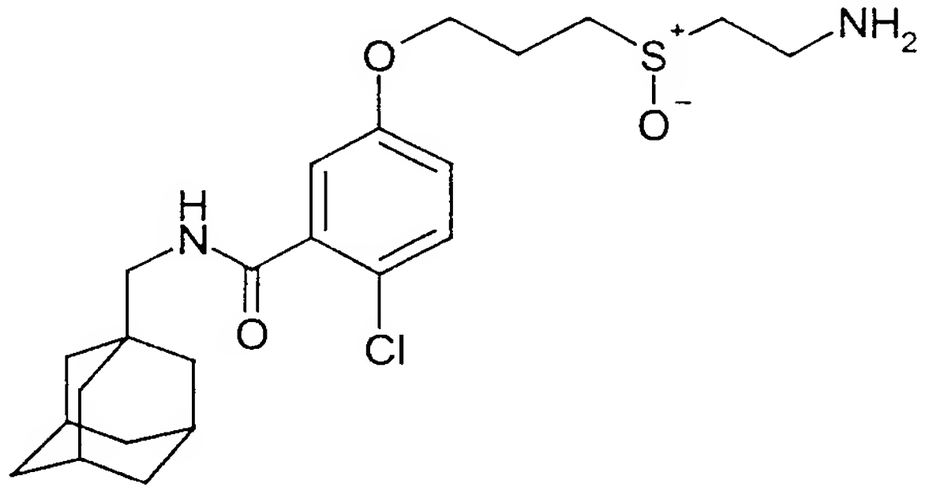
Prepared according to the method of Example 11c from [2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-propylthio]ethyl]-carbamic acid, 1,1-dimethylethyl ester (Example 24a, 0.34g), to afford the title compound (0.065g).

MS (APCI +ve) 437/439 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.29 (1H, t); 7.94 (3H, s); 7.37 (1H, d); 7.00 (1H, dd); 6.92 (1H, d); 4.07 (2H, t); 2.98 (2H, t); 2.92 (2H, d); 2.71 (2H, t); 2.66 (2H, t); 2.02-1.95 (5H, m); 1.63 (6H, q); 1.52 (6H, s).

Example 25

(±)-5-[3-(2-Aminoethylsulfinyl)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



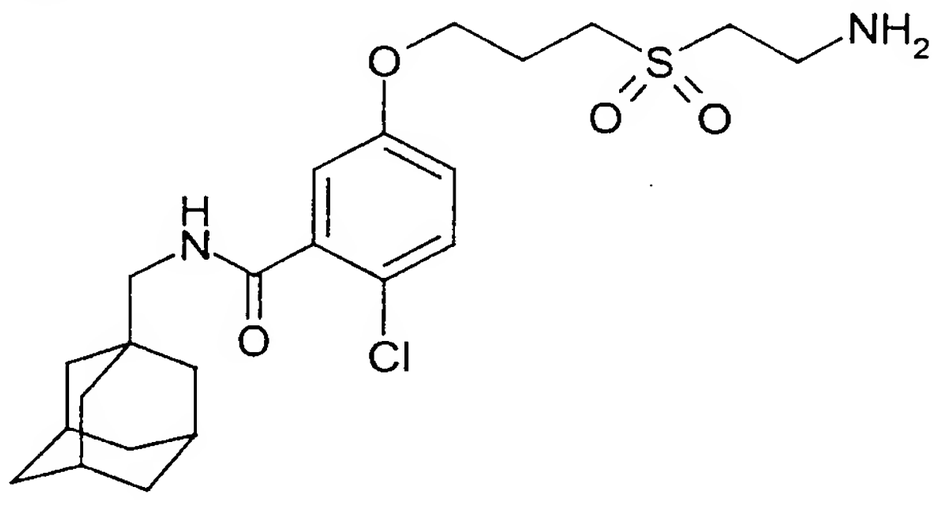
Prepared according to the method of Example 22 from [2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-propylthio]ethyl]-carbamic acid, 1,1-dimethylethyl ester (Example 24a, 0.3g), to give the title compound (0.16g).

MS (APCI +ve) 453/455 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.30 (1H, t); 8.05 (3H, s); 7.38 (1H, d); 7.01 (1H, dd); 6.93 (1H, d); 4.13 (2H, t); 3.30-2.87 (8H, m); 2.10 (2H, quin); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s).

Example 26

5-[3-(2-Aminoethylsulfonyl)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



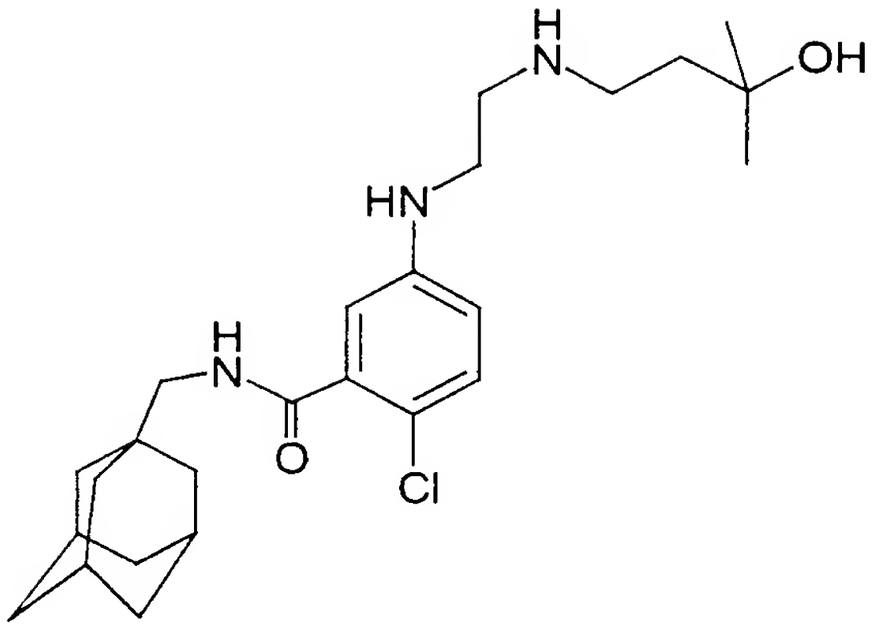
Prepared according to the method of Example 23 using [2-[3-[4-chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethylcarbamoyl)-phenoxy]-propylthio]ethyl]-carbamic acid, 1,1-dimethylethyl ester (Example 24a, 0.2g), to give the title compound (0.07g).

MS (APCI +ve) 469/471 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.30 (1H, t); 8.12 (3H, s); 7.39 (1H, d); 7.02 (1H, dd); 6.94 (1H, d); 4.15 (2H, t); 3.60-3.20 (6H+water, m); 2.92 (2H, d); 2.12 (2H, quin); 1.94 (3H, s); 1.63 (6H, q); 1.53 (6H, s).

Example 27

2-Chloro-5-[[2-[(3-hydroxy-3-methylbutyl)amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



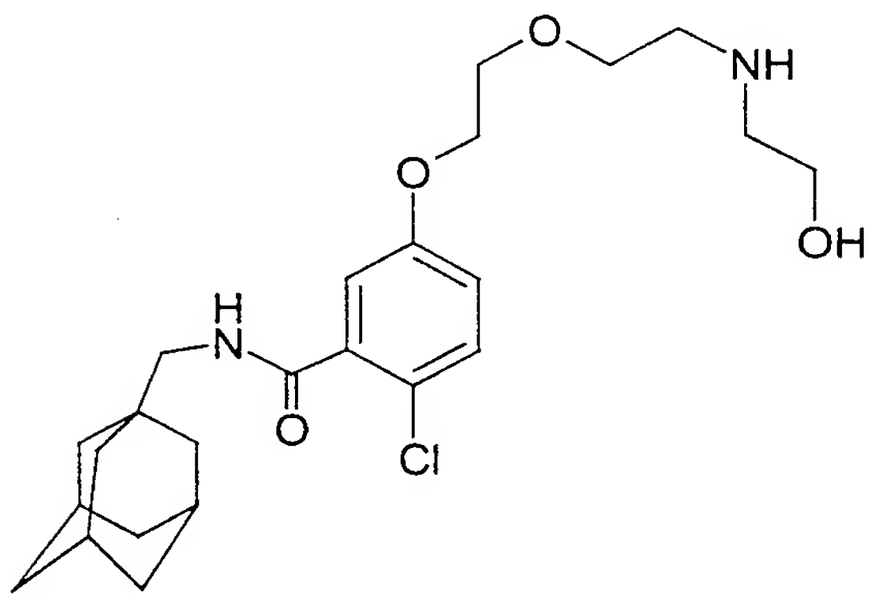
Prepared according to the method described in Example 1

MS (APCI +ve) 448/450 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.15 (1H, t); 7.10 (1H, d); 6.60-6.50 (2H, m); 5.86 (1H, t); 3.06 (2H, q); 2.89 (2H, d); 2.73-2.60 (4H, m); 1.93 (3H, s); 1.63 (6H, q); 1.52 (6H, s); 1.08 (6H,s).

Example 28

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride



a) 2-Chloro-5-[2-[2-chloroethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

Prepared according to the method of Example 11a from 2-chloro-5-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (WO99/29661, 1.0g), 2-(2-

chloroethoxy)ethanol (0.5ml), triphenylphosphine (1.0g) and diethylazadicarboxylate (0.7ml). Chromatography eluting with isohexane/ethyl acetate 4:1 to 7:3 gave the sub-title product as a solid (1.2g).

MS (APCI +ve) 426/428/430 $(M+H)^+$

^{1}H NMR (CDCl3) δ 7.30-7.26 (2H, m); 6.93 (1H, dd); 6.33 (1H, t); 4.20 (2H, t); 3.88 (2H, t); 3.82 (2H, t); 3.65 (2H, t); 3.17 (2H, d); 2.00 (3H, s); 1.68 (6H, q); 1.58 (6H, s).

b) 2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

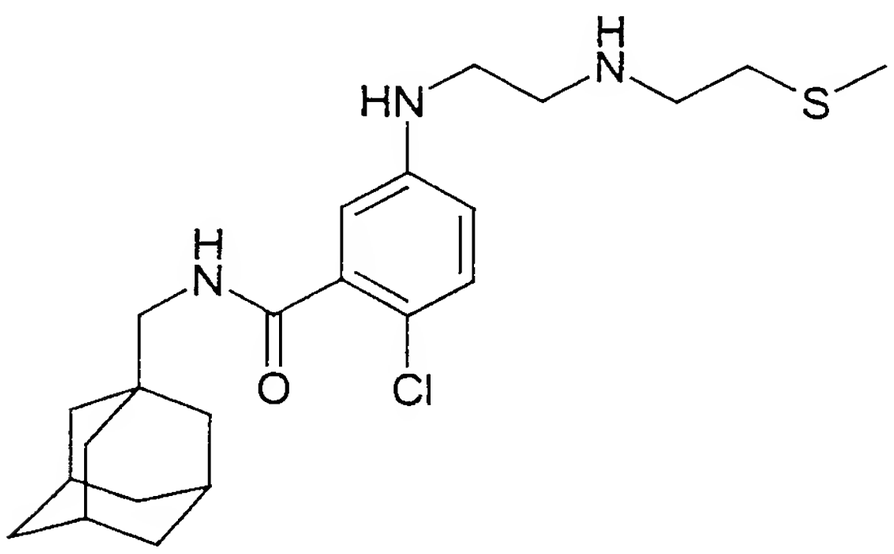
2-Hydroxyethylamine (0.15ml) was added to a mixture of 2-chloro-5-[2-[2-chloroethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.1g, Example 28a), potassium iodide (0.005g) and triethylamine (0.5ml) in n-butanol (4ml). The mixture was heated in a sealed tube at 100°C for 24h. After cooling, the reaction mixture was partitioned between ethyl acetate and water. The organics were separated and washed with water, then with saturated sodium hydrogencarbonate solution followed by brine. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated. Purification by RP-HPLC eluting with a gradient of methanol / 0.1% aqueous trifluoroacetic acid. Concentration gave the product as the trifluoroacetate salt, which was converted to the hydrochloride by treatment with 4M HCl in 1,4-dioxane to give the title product (0.030g).

MS (APCI +ve) 451/453 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.62 (2H, brs); 8.29 (1H, t); 7.37 (1H, d); 7.01 (1H, dd); 6.93 (1H, d); 4.16 (2H, t); 3.85-3.70 (4H, m); 3.65 (2H, t); 3.17 (2H, quin); 3.02 (2H, quin); 2.92 (2H, d); 1.94 (3H, s); 1.63 (6H, q); 1.52 (6H, s).

Example 29

2-Chloro-5-[[2-[[2-(methylthio)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



a) 2-Chloro-5-nitro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

To a solution of 2-chloro-5-nitrobenzoic acid (1.22g) in *N,N*-dimethylformamide (1.5 ml) was added 1,1-carbonyldiimidazole (1.0 g). The resulting reaction mixture was stirred for 2.5h and then 1-adamantanemethylamine (1.0g) was added. After 14h the reaction mixture was partitioned between ethyl acetate and water and the organic layer was separated, washed with water and brine and then dried over sodium sulphate (Na_2SO_4). The organic layer was concentrated under reduced pressure to give a residue which was purified by silica gel chromatography (eluting with 3-10% methanol in dichloromethane) to yield the sub-title compound as a yellow solid (1.7 g).

MS (APCI +ve) 348/350 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 8.53 (1H, d), 8.2 (1H, dd), 7.6 (1H, d), 6.2 (1H, bs), 3.2 (2H, d), 2.0 (3H, bs), 1.8 (12H, m)

b) 5-Amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

A solution of 2-chloro-5-nitro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 29a, 0.50 g) and ammonium chloride (0.5g) were dissolved in 50% aqueous ethanol. Iron powder (0.5g) was added and the mixture stirred at reflux temperature for 3h before being cooled and the solids removed by filtration. The mother liquors were treated

with 10% sodium hydroxide solution and the product extracted into ethyl acetate. The organic solution was washed with brine, dried over sodium sulphate (Na_2SO_4) and concentrated to give a residue which was purified by silica gel chromatography to give the sub-title compound as a white solid (0.4g).

MS (APCI +ve) 319/321 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.14 (1H, t); 7.03 (1H, dd); 6.56 (2H, m); 5.36 (2H, s); 2.89 (2H, d); 1.95 (3H, s); 1.7 (12H, m)

c) 2-Chloro-5-[(2-chloroethyl)amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

5-Amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (7 g, Example 29b) and chloroacetaldehyde (50% solution in water, 6.6 ml) were stirred in methanol (120 ml) under nitrogen for 10 min. A mixture of 6M hydrochloric acid (1.8 ml) and methanol (1.8 ml) was added, followed by sodium cyanoborohydride (1.48 g). The mixture was stirred for 2.5h. The methanol was then removed under reduced pressure and the residue partitioned between saturated aqueous sodium hydrogencarbonate and dichloromethane. The aqueous layer was extracted twice more with dichloromethane and the combined extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the sub-title compound (8.2 g).

MS (APCI +ve) 381/383/385 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.18 (1H, d); 7.02-6.99 (1H, m); 6.64-6.61 (1H, m); 6.37 (1H, br s); 4.19 (1H, br t); 3.72-3.69 (2H, m); 3.53-3.49 (2H, m); 3.17 (2H, d); 2.01 (3H, br s); 1.69 (6H, m); 1.59 (6H, br s).

d) 2-Chloro-5-[[2-[[2-(methylthio)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

2-Chloro-5-[(2-chloroethyl)amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.200 g, Example 29c), 2-(methylthio)ethylamine (0.478 g), triethylamine (0.7 ml) and

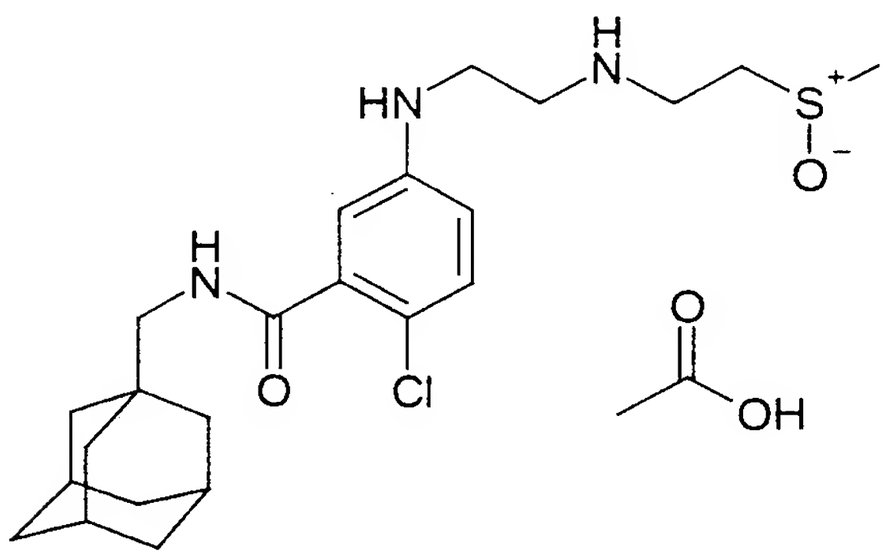
tetrahydrofuran (4 ml) were heated together in a sealed tube at 80^{0}C for 24h. The mixture was cooled, poured into saturated aqueous sodium hydrogencarbonate solution and extracted into ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (eluant 19:1 / dichloromethane:methanol) to afford the title compound as a gum (0.129 g).

MS (APCI +ve) 436/438 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.15 (1H, d); 6.97 (1H, d); 6.60 (1H, dd); 6.33 (1H, br t); 4.41 (1H, br t); 3.21-3.16 (4H, m); 2.91-2.82 (4H, m); 2.66 (2H, t); 2.17 (3H, s); 2.00 (3H, br s); 1.69 (6H, m); 1.58 (6H, br s).

Example 30

2-Chloro-5-[[2-[[2-(methylsulfinyl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetic acid salt



a) [2-[[4-Chloro-3-[[(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]-phenyl]amino]ethyl][2-(methylthio)ethyl]-carbamic acid, 1,1-dimethylethyl ester

2-Chloro-5-[[2-[[2-(methylthio)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 29d, 0.284 g), di-*t*-butyldicarbonate (0.284 g), triethylamine (0.2 ml) and dichloromethane (5 ml) were stirred together under nitrogen for 48h, then poured into water and extracted into ethyl acetate. The combined extracts were

dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the sub-title compound (0.330 g) as an oil.

MS (APCI +ve) 536/538 $(M+H)^+$

b) [2-[[4-Chloro-3-[[(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl]-amino]ethyl][2-(methylsulfinyl)ethyl]-carbamic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 22 from [2-[[4-chloro-3-[[(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl]amino]ethyl][2-(methylthio)ethyl]-carbamic acid, 1,1-dimethylethyl ester (0.460 g, Example 30a), 3-chloroperoxybenzoic acid (0.315 g) and dichloromethane (20 ml). Excess calcium hydroxide was added, followed by excess magnesium sulfate. The mixture was filtered through celite and concentrated under reduced pressure. The crude material was purified on silica gel (19:1 / dichloromethane:methanol) to afford the sub-title compound as a gum (0.141 g) and the corresponding sulfone (0.057 g).

MS (APCI +ve) 552/554 $(M+H)^+$

c) 2-Chloro-5-[[2-[[2-(methylsulfinyl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetic acid salt

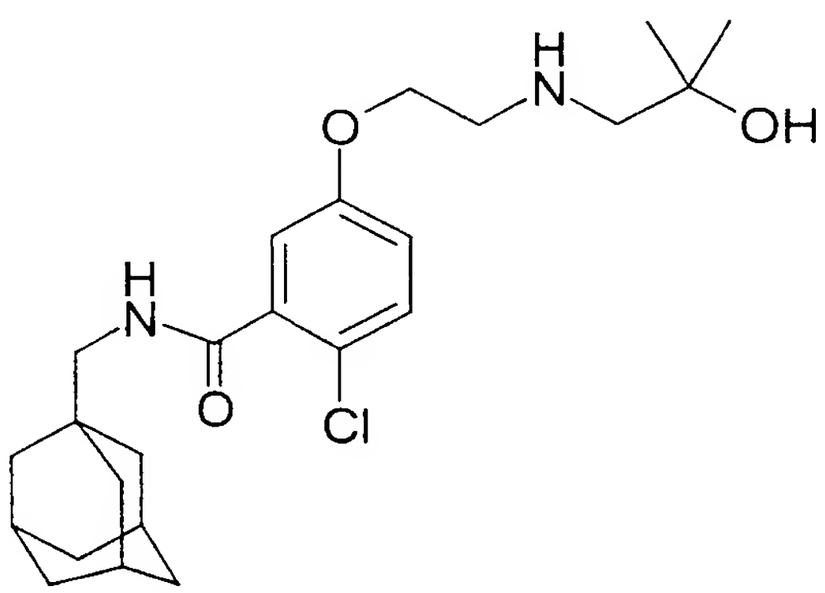
[2-[[4-Chloro-3-[[(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl]-amino]ethyl][2-(methylsulfinyl)ethyl]-carbamic acid, 1,1-dimethylethyl ester (0.141 g, Example 30b), 4M hydrogen chloride in 1,4-dioxane (10 ml) and methanol (10 ml) were stirred together under nitrogen for 3h. The mixture was poured into 25% aqueous ammonia solution and concentrated under reduced pressure to give the free base. This was purified by column chromatography over silica gel (eluting with 19:1:0.1 / dichloromethane:methanol:ammonia), and the resulting oil repurified by RPHPLC (eluant NH_4OAc: CH_3CN / 75%:25% to 5%:95% gradient) to afford the title compound (0.030 g).

MS (APCI +ve) 452/454 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.15 (1H, d); 6.96 (1H, m); 6.62-6.59 (1H, m); 6.36 (1H, br t); 3.23-3.07 (6H, m); 2.93-2.78 (4H, m); 2.62 (3H, s); 2.00 (3H, br s); 1.69 (6H, m); 1.58 (6H, s).

Example 31

2-Chloro-5-[2-[(2-hydroxy-2-methylpropyl)amino]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide, dihydrochloride



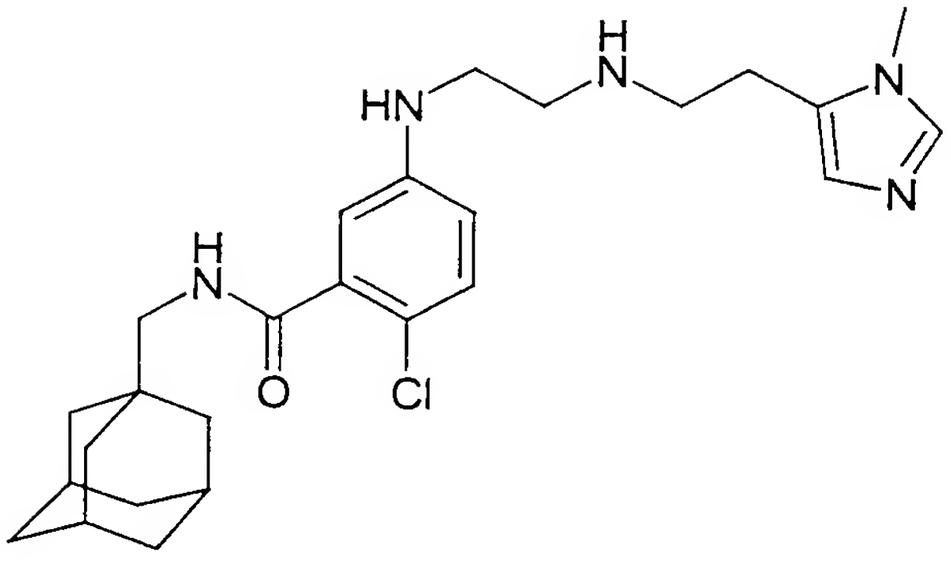
Prepared from 2-chloro-5-[2-[2-chloroethoxy]ethoxy]-*N*-(tricyclo[3.3.1.13,7]dec-1-ylmethyl)-benzamide (0.380g, Example 28a) according to the procedure described in Example 28b to afford the title compound as a solid (0.038g)

MS (APCI +ve) 435/437 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.71-8.40 (2H, m), 8.33 (1H t, J = 6.2 Hz), 7.43 (1H, d, J = 8.7), 7.05 (2H, dd, J = 8.7, 3.0 Hz), 6.99 (1H, d, J = 3.1 Hz,), 5.21 (1H, S), 4.31 (2H, t, J = 5.2 Hz), 3.46-3.23 (2H, m), 2.99 (3H, d, J = 5.8 Hz), 2.93 (3H, d, J = 6.3 Hz), 1.94 (3H, s), 1.63 (6H, m), 1.52 (s, 6H), 1.28 (s, 6H)

Example 32

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-5-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



a) 2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-5-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

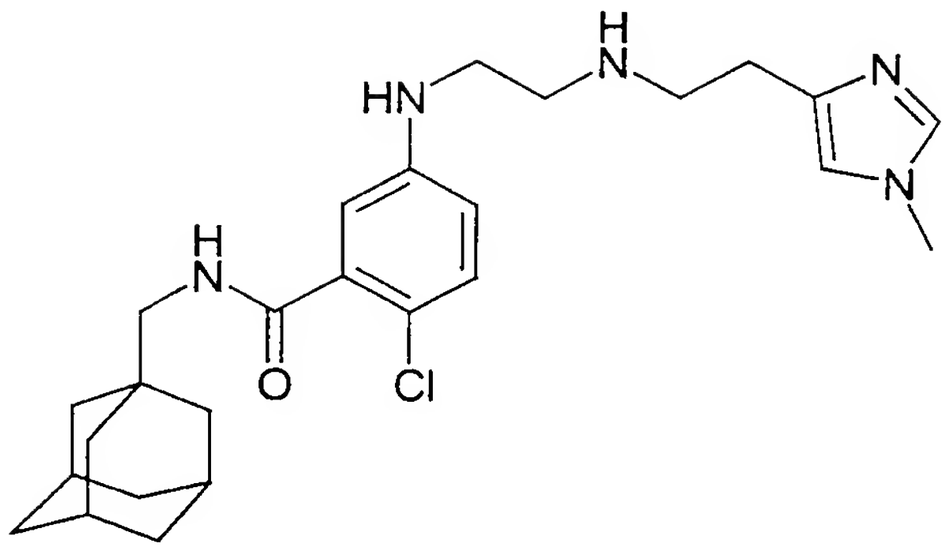
2-Chloro-5-[(2-chloroethyl)amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 29c, 0.100 g), 3-methylhistamine (0.200 g), *N,N*-diisopropylethylamine (0.5 ml), potassium iodide (0.040 g) and n-butanol (4 ml) were heated together in a sealed tube at 110^{0}C for 24h. The solution was cooled, poured into saturated aqueous sodium hydrogencarbonate solution and extracted into ethyl acetate. The extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (eluant 19:1:0.1 dichloromethane/methanol/ammonia) to afford the title compound as a gum (0.053 g).

MS (APCI +ve) 470/472 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.37 (1H, s); 7.15 (1H, d); 6.93-6.92 (1H, m); 6.75 (1H, s); 6.61-6.57 (2H, m); 4.31 (1H, br t); 3.56 (3H, s); 3.23-3.16 (4H, m); 2.89 (4H, t); 2.75 (2H, t); 2.00 (3H, br s); 1.69 (6H, m); 1.59 (6H, brs).

Example 33

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



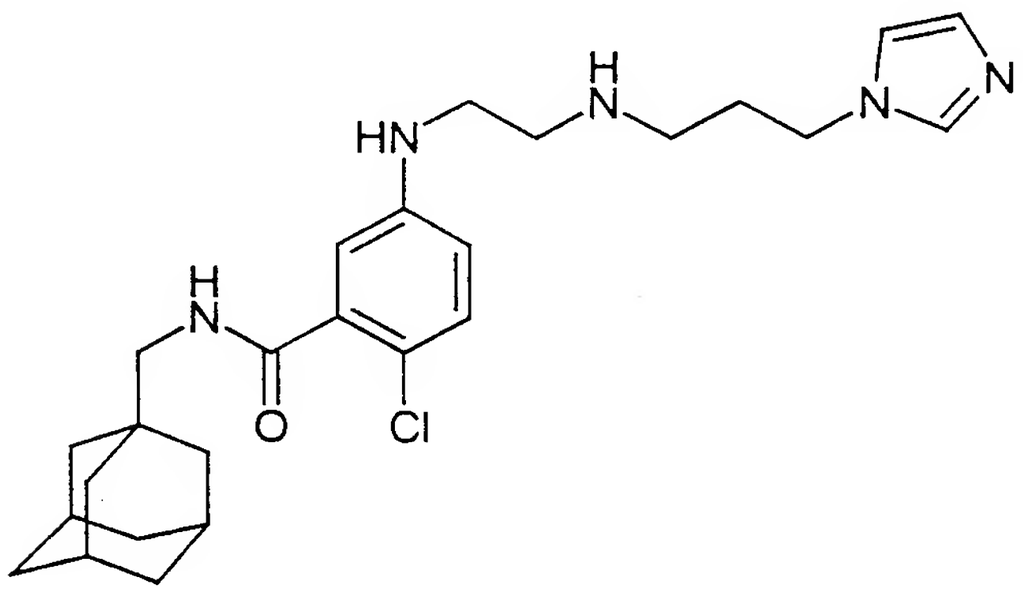
Prepared as in Example 32 using 2-chloro-5-[(2-chloroethyl)amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 29c, 0.200 g), 1-methylhistamine (0.400 g), *N,N*-diisopropylethylamine (1 ml), potassium iodide (0.080 g) and n-butanol (4 ml) to give the title compound as a gum (0.040 g).

MS (APCI +ve) 470/472 $(M+H)^+$

^{1}H NMR ($CDCl_3$) δ 7.34 (1H, s), 7.13 (1H, d); 6.94 (1H, d); 6.34 (1H s); 6.57 (1H, dd); 6.37 (1H, br t); 4.56 (1H, br t); 3.62 (3H, s); 3.20-3.15 (4H, m); 2.93-2.87 (4H, m); 2.73 (2H, t); 2.00 (3H, br s); 1.69 (6H, m); 1.58 (6H, s).

Example 34

2-Chloro-5-[[2-[[3-(1*H*-imidazol-1-yl)propyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



2-Chloro-5-[(2-chloroethyl)amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (Example 29c, 0.200 g), *N*-(3-aminopropyl)-imidazole (0.957 g), triethylamine (1.2 ml), sodium iodide (0.010 g) and tetrahydrofuran (4 ml) were heated together in a sealed tube at 80^{0}C for 24h. The solution was cooled, poured into saturated aqueous sodium hydrogencarbonate solution and extracted into ethyl acetate. The extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (eluant 19:1:0.1 dichloromethane /methanol /ammonia) to afford the title compound as a gum (0.176 g).

MS (APCI +ve) 470/472 $(M+H)^+$

^{1}H NMR (d6-DMSO) δ 8.18 (1H, t); 7.58 (1H, s); 7.14-7.10 (2H, m); 6.86 (1H, s); 6.60-6.57 (2H, m); 5.85 (1H, t); 4.00 (2H, t); 3.07-3.06 (2H, m); 2.90-2.89 (2H, m); 2.67-2.65 (2H, m); 2.46-2.43 (2H, m); 1.93 (3H, br s); 1.85-1.78 (2H, m); 1.64 (6H, br m); 1.51 (6H, br s).

Pharmacological Analysis

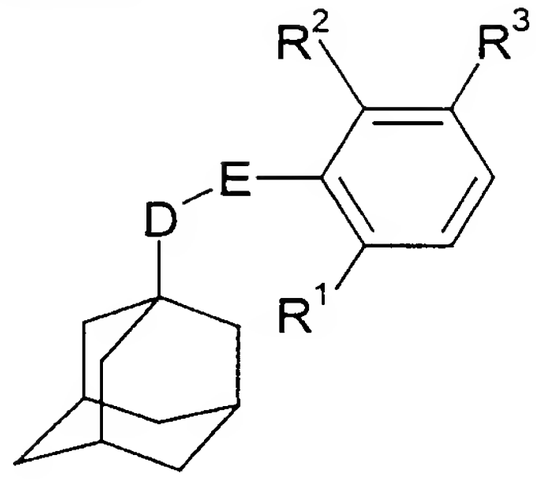
Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the $P2X_7$ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound on the $P2X_7$ receptor.

In this manner, each of the title compounds of Examples 1 to 34 was tested for antagonist activity at the $P2X_7$ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 μl of test solution comprising 200 μl of a suspension of THP-1 cells (2.5 x 10^6 cells/ml) containing 10^{-4}M ethidium bromide, 25 μl of a high potassium buffer solution containing 10^{-5}M bbATP, and 25 μl of the high potassium buffer solution containing 3 x 10^{-5}M test compound. The plate was

covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and pyridoxal 5-phosphate (a $P2X_7$ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC_{50} figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of Examples 1 to 34 demonstrated antagonist activity, having a pIC_{50} figure > 5.0.

CLAIMS

1. A compound of general formula



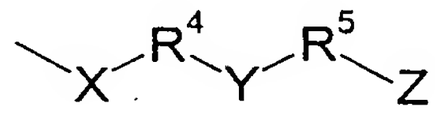
(I)

wherein D represents CH_2 or CH_2CH_2;

E represents C(O)NH or NHC(O);

R^1 and R^2 each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1-C_6 alkyl or trifluoromethyl group;

R^3 represents a group of formula



(II);

X represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y represents an oxygen or sulphur atom or a group NR^{11}, SO or SO_2;

Z represents a group -OH, -SH, $-CO_2H$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^6R^7$, $-C(O)NR^8R^9$, imidazolyl, 1-methylimidazolyl, $-N(R^{10})C(O)$-C_1-C_6 alkyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyloxy, $-OC(O)NR^{12}R^{13}$, $-OCH_2OC(O)R^{14}$, $-OCH_2OC(O)OR^{15}$ or $-OC(O)OCH_2OR^{16}$;

R^4 represents a C_2-C_6 alkyl group;

R^5 represents a C_1-C_6 alkyl group;

R^6, R^7, R^8, R^9, R^{10}, R^{12} and R^{13} each independently represent a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one hydroxyl group;

R^{11} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14}, R^{15} and R^{16} each independently represent a C_1-C_6 alkyl group;

with the provisos that (i) when E represents NHC(O), X represents O, S or NH and Y represents O, then Z represents $-NR^6R^7$ where R^6 represents a hydrogen atom and R^7 represents either a hydrogen atom or a C_1-C_6 alkyl group substituted by at least one hydroxyl group, and (ii) when E represents NHC(O), X represents O, S or NH, Y represents NH and R^5 represents CH_2CH_2, then Z is not -OH or imidazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein D represents CH_2.

3. A compound according to claim 1 or claim 2, wherein E represents NHC(O).

4. A compound according to any one of claims 1 to 3, wherein R^1 and R^2 each independently represent a hydrogen, chlorine or bromine atom, or an amino, nitro, C_1-C_3 alkyl or trifluoromethyl group.

5. A compound according to any one of the preceding claims, wherein X represents an oxygen atom or a group NH.

6. A compound according to any one of the preceding claims, wherein Y represents a group NR^{11}.

7. A compound according to claim 6, wherein R^{11} represents a hydrogen atom.

8. A compound according to any one of the preceding claims, wherein Z represents a group -OH, $-CO_2H$, methoxy, methylthio, methylsulphinyl, methylsulphonyl, $-NR^6R^7$, imidazolyl, 1-methylimidazolyl, $-C(O)NR^8R^9$, $-N(R^{10})C(O)CH_3$, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkoxycarbonyloxy, $-OC(O)NR^{12}R^{13}$, $-OCH_2OC(O)R^{14}$, $-OCH_2OC(O)OR^{15}$ or $-OC(O)OCH_2OR^{16}$.

9. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, according to claim 1 which is selected from:

2-Chloro-5-[2-(2-methoxyethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethyamino]-acetic acid, hydrochloride,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

5-[2-(2-Aminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

5-[2-(2-Acetylaminoethylamino)ethylamino]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

[2-[4-Chloro-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)carbamoyl-phenylamino]-ethylamino]-propionic acid,

2-Chloro-5-[2-(2-methylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

2-Chloro-5-[2-(2-dimethylcarbamoylethylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate,

2-Chloro-5-[3-(3-hydroxypropylthio)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-[2-(2-Aminoethylthio)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[2-(3-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[3-(3-hydroxypropylsulfonyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(±)-2-Chloro-5-[3-(3-hydroxypropylsulfinyl)propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylthio)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(S)-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(R)-2-Chloro-5-[2-(2-hydroxypropylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(S)-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(R)-2-Chloro-5-[2-(2-hydroxy-1-methylethylamino)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(±)-2-Chloro-5-[2-(3-hydroxypropylsulfinyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

(±)-5-[2-(2-Aminoethylsulfinyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-[2-(2-Aminoethylsulfonyl)ethoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-[3-(2-Aminoethylthio)propoxy]-2-chloro- *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

(±)-5-[3-(2-Aminoethylsulfinyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-[3-(2-Aminoethylsulfonyl)propoxy]-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[[2-[(3-hydroxy-3-methylbutyl)amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

2-Chloro-5-[[2-[[2-(methylthio)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(methylsulfinyl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetic acid salt,

2-Chloro-5-[2-[(2-hydroxy-2-methylpropyl)amino]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide, dihydrochloride,

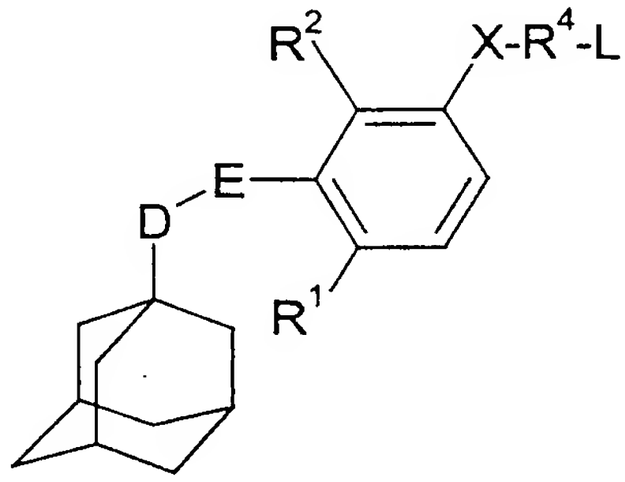
2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-5-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, and

2-Chloro-5-[[2-[[3-(1*H*-imidazol-1-yl)propyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide.

10. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

a) when Y represents an oxygen or sulphur atom or a group NR^{11}, reacting a compound of general formula



(III)

wherein L represents a leaving group and D, E, R^1, R^2, X and R^4 are as defined in formula (I), with a compound of general formula

$$R^{20}—R^5—Z \quad \text{(IV)}$$

wherein R^{20} represents –OH, -SH or –NHR^{11} and R^5, R^{11} and Z are as defined in formula (I); or

b) when Y represents SO or SO_2, reacting a corresponding compound of formula (I) in which Y represents a sulphur atom with a suitable oxidising agent;

and optionally after (a) or (b) converting the compound of formula (I) obtained to a pharmaceutically acceptable salt or solvate thereof.

11. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A process for the preparation of a pharmaceutical composition as claimed in claim 11 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 9 with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 for use in therapy.

14. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 for use in the treatment of rheumatoid arthritis.

15. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 for use in the treatment of chronic obstructive pulmonary disease.

16. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in therapy.

17. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in treating rheumatoid arthritis.

18. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease.

19. A method of effecting immunosuppression which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 to a patient in need thereof.

20. A method of treating rheumatoid arthritis which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 to a patient in need thereof.

21. A method of treating chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02418

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 235/46, C07C 237/30, C07C 233/65, C07C 233/01, C07C 233/88, A61K 31/166, A61K 31/167, A61P 37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9929661 A1 (ASTRA AKTIEBOLAG), 17 June 1999 (17.06.99), see the claims (esp. claim 5) and examples 71 and 77 --	1-21
X	WO 9929660 A1 (ASTRA AKTIEBOLAG), 17 June 1999 (17.06.99), the claims --	1-21
P,X	WO 0061569 A1 (ASTRAZENECA AB), 19 October 2000 (19.10.00), the claims --	1-21

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2001	20 -03- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02418

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Medicinal Chemistry, Volume 15, No 11, 1972, V.L. Narayanan, "Adamantyl Analogs of 2-(3-Dimethylaminopropylthio)cinnamanilide" page 1180 - page 1182 -- --------	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02418

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **19-21**
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02418

Claims 19-21 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/02418

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9929661 A1	17/06/99	AU 1791399 A	28/06/99
		BR 9813390 A	03/10/00
		EP 1036059 A	20/09/00
		NO 20002786 A	31/07/00
		SE 9704544 D	00/00/00
WO 9929660 A1	17/06/99	AU 1791499 A	28/06/99
		BR 9813368 A	03/10/00
		CN 1280560 T	17/01/01
		EP 1036058 A	20/09/00
		NO 20002785 A	01/08/00
		SE 9704545 D	00/00/00
WO 0061569 A1	19/10/00	AU 3994700 A	14/11/00
		GB 0002330 D	00/00/00
		AU 4950499 A	07/02/00
		NO 20010211 D	00/00/00
		SE 9901270 D	00/00/00